

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 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.

Not recommended regimens are clearly inferior compared to recommended and alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer treatment duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection.

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](#)

Last update: September 21, 2017

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 infection.

Approximately 10% to 15% of genotype 1-infected 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 infection, 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-infected 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 an increased risk 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 infection.



- [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 Genotype 1 Patients](#)

Last update: September 21, 2017

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

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

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

| RECOMMENDED | DURATION | RATING  |
|---|----------|--|
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs ^a for elbasvir | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b | 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 |
| ALTERNATIVE | DURATION | RATING  |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), and weight-based ribavirin | 12 weeks | I, A |
| Daily simeprevir (150 mg) plus sofosbuvir (400 mg) | 12 weeks | I, A |
| Daily daclatasvir (60 mg) ^c plus sofosbuvir (400 mg) | 12 weeks | I, B |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs ^a for elbasvir | 16 weeks | IIa, B |

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

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

^c The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

Recommended Regimens

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-infected patients treated for 12 weeks without ribavirin had an overall SVR12 rate 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-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% (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 rate in treatment-experienced, genotype 1a-infected 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-infected 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. 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 infection without 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 infection, 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 rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR 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 infection 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-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. 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-infected, 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%).

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir + Ribavirin

In the SAPPHERE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed ([Zeuzem, 2014](#)). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin ([Andreone, 2014](#)). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naïve or -experienced without cirrhosis ([Kwo, 2016](#)). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure ([Foster, 2015](#)); ([Pol, 2017](#)); ([Foster, 2016](#)). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and

sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).



Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

Last update: May 24, 2018

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^a

| RECOMMENDED | DURATION | RATING  |
|--|----------|--|
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs ^b 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) ^c | 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 |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs ^b for elbasvir | 16 weeks | I, B |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

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

^c This is a 3-tablet coformulation. 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-infected patients treated for 12 weeks without ribavirin had an overall SVR 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 (SVR with cirrhosis 95% [19/20]; SVR 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](#)).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected 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 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-infected 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. 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 infection 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-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. 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-infected, 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-infected patients. The single treatment failure occurred in a patient with genotype 1a infection 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 Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected 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-naïve or -experienced, genotype 1-infected 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-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

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-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC₅₀) detected at a 1% level resulted in a lower SVR12 rate 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-infected, 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.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10⁹/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 ([Feld, 2016](#)). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a [warning](#) in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.)

Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed



with the patient. If the decision is made to initiate treatment with paritaprevir/ritonavir/ombitasvir \pm dasabuvir, close monitoring of total and direct bilirubin and transaminase levels every 1 to 2 weeks for the first 4 weeks of therapy is recommended to ensure early detection of drug-induced liver injury. Educating patients about the importance of reporting systemic symptoms, such as jaundice, weakness, and fatigue, is also strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is suspected. If a patient is already taking paritaprevir/ritonavir/ombitasvir \pm dasabuvir and tolerating the regimen, laboratory monitoring as noted without discontinuation of treatment is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided during the first 4 weeks of therapy with paritaprevir/ritonavir/ombitasvir \pm dasabuvir in patients with compensated cirrhosis, use of these regimens is not recommended.

Last update: May 24, 2018

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

Recommended and alternative 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) ^a | 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 |
| ALTERNATIVE | DURATION | RATING  |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) | 12 weeks | I, A |
| Daily simeprevir (150 mg) plus sofosbuvir (400 mg) | 12 weeks | I, A |
| Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) | 12 weeks | I, B |

^a This is a 3-tablet coformulation. Please refer to the prescribing information.

^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

Recommended Regimens

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-infected 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](#)). 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-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% (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 rate in treatment-experienced, genotype 1a-infected 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-infected 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. 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 infection without 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 infection, 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 rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR 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 infection 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-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. 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-infected, 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%).

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

In the SAPPHERE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed ([Zeuzem, 2014](#)). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin ([Andreone, 2014](#)). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naïve or -experienced without cirrhosis ([Kwo, 2016](#)). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure ([Foster, 2015](#)); ([Pol, 2017](#)); ([Foster, 2016](#)). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).

Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-



treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

Last update: September 21, 2017

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^a

| 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) ^b | 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 |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) ^c | 12 weeks | I, A |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

^c Please see statement on FDA [warning](#) regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

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-infected patients treated for 12 weeks without ribavirin had an overall SVR 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 (SVR with cirrhosis 95% [19/20]; SVR 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](#)).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected 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 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-infected 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. 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 infection 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-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. 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-infected, 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-infected patients. The single treatment failure occurred in a patient with genotype 1a infection 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 Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected 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-naïve or -experienced, genotype 1-infected 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-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

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-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC₅₀) detected at a 1% level resulted in a lower SVR12 rate 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-infected, 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.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10⁹/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 ([Feld, 2016](#)). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a [warning](#) in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.)

Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with paritaprevir/ritonavir/ombitasvir ± dasabuvir, close



monitoring of total and direct bilirubin and transaminase levels every 1 to 2 weeks for the first 4 weeks of therapy is recommended to ensure early detection of drug-induced liver injury. Educating patients about the importance of reporting systemic symptoms, such as jaundice, weakness, and fatigue, is also strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is suspected. If a patient is already taking paritaprevir/ritonavir/ombitasvir \pm dasabuvir and tolerating the regimen, laboratory monitoring as noted without discontinuation of treatment is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided during the first 4 weeks of therapy with paritaprevir/ritonavir/ombitasvir \pm dasabuvir in patients with compensated cirrhosis, use of these regimens is not recommended.

Last update: September 21, 2017

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

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

NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

| 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) ^a | 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 ^b 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 ^b for elbasvir | 16 weeks | IIa, B |
| <p>^a This is a 3-tablet coformulation. Please refer to the prescribing information.</p> <p>^b Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.</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-infected 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-infected 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 infection 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 similarly high SVR rates 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-infected 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 (which 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

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-infected 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 rate 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-infected patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency.

Last update: September 21, 2017

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^a

| 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) ^b | 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 RAS ^c for elbasvir | 12 weeks | IIa, B |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RAS ^c for elbasvir | 16 weeks | IIa, B |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

^c Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer [antiviral resistance](#).

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 infection 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-infected, treatment-experienced patients was 99.1% (109/110), with 100% (78/78) in patients with genotype 1a infection and 96.9% (31/32) among those with genotype 1b infection. 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 SVR rates 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-infected 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 (which 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-infected 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-infected 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-infected 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 rate 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: September 21, 2017

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) ^a , regardless of subtype | 12 weeks | Ila, B |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients | 12 weeks | Ila, 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 | Ila, B |

^a This is a 3-tablet coformulation. 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 infection 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 infection 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 infection 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 infection 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 infection. Forty-four patients with genotype 1a infection, 22 with genotype 1b infection, 33 with genotype 2 infection, and 52 with genotype 3 infection were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a-infected patients and 8 were in those with genotype 3 infection. One genotype 1b-infected patient and a single genotype 2-infected 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-infected patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b-infected 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 infection, 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, high SVR rates were noted when patients were retreated with ledipasvir/sofosbuvir for 12 weeks ([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 infection. One virologic failure was observed in a patient determined to have genotype 3 infection prior to retreatment ([Wyles, 2015b](#)).

Last update: September 21, 2017

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^a

| 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) ^b , 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 |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b This is a 3-tablet coformulation. 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 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 infection 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 infection 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 \pm ribavirin and 11 were previously treated with sofosbuvir and ribavirin \pm peginterferon. Overall, 99% (145/146) of patients achieved SVR 12. The single patient who did not respond to therapy had genotype 1a infection 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 infection. Forty-four patients with genotype 1a infection, 22 with genotype 1b infection, 33 with genotype 2 infection, and 52 with genotype 3 infection were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a-infected patients and 8 were in those with genotype 3 infection, and most of these patients had cirrhosis. One genotype 1b-infected patient and a single genotype 2-infected 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-infected patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b-infected patients who had specifically experienced a prior non-NS5A inhibitor sofosbuvir-containing regimen failure (n=12), and no virologic failures.

Last update: September 21, 2017

NS5A Inhibitor DAA-Experienced Genotype 1 Patients

Recommended and alternative regimens for:

NS5A Inhibitor DAA-Experienced, Genotype 1 Patients With or Without Compensated Cirrhosis^a **i**

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

^a For [decompensated cirrhosis](#), please refer to the appropriate section.
^b This is a 3-tablet coformulation. 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 rate was 97% (146/150) in genotype 1-infected patients. SVR12 rates were 96% (97/101) for participants with genotype 1a infection and 100% (45/45) for those with genotype 1b infection. A single genotype 1-infected patient experienced relapse; this individual had subtype 1a infection and cirrhosis. Baseline RASs and the presence of cirrhosis were not significant predictors of virologic failure in genotype 1 infection. Serious adverse events were similar between 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-infected 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 and 79% were genotype 1a infected. 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 SVR 12. 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: September 21, 2017

Treatment-Experienced Genotype 2

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



- [Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis](#)
- [Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis](#)
- [DAA-Experienced \(Including NS5A Inhibitors\), Genotype 2 Patients With or Without Compensated Cirrhosis](#)

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis

Recommended and alternative 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) ^a | 8 weeks | I, A |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, A |
| ALTERNATIVE | DURATION | RATING  |
| Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) | 12 weeks | Ila, B |

^a This is a 3-tablet coformulation. Please refer to the prescribing information.

^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

Recommended Regimens

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 patients with genotype 2, 4, 5, or 6 infection without cirrhosis who were treatment-naïve or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) ([Asselah, 2018b](#)). One hundred forty-five genotype 2-infected 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-infected 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-infected 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 infection, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir



Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks to 24 weeks has been shown to have efficacy in genotype 2 infection. However, available data in patients previously treated with peginterferon/ribavirin are very limited ([Wyles, 2015](#)); ([Sulkowski, 2014a](#)). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult-to-treat patients, such as those with cirrhosis.

Last update: September 21, 2017

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

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

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

| 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) ^b | 12 weeks | I, B |
| ALTERNATIVE | DURATION | RATING  |
| Daily daclatasvir (60 mg) ^c plus sofosbuvir (400 mg) | 16 to 24 weeks | Ila, B |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

^c The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

Recommended Regimens

Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2-infected 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 sofosbuvir/velpatasvir/voxilaprevir or 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2-infected 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 infection, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

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

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 infection 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-infected 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 $<100 \times 10^9/L$ 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. This is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks to 24 weeks has been shown to have efficacy in genotype 2 infection. However, available data in patients previously treated with peginterferon/ribavirin are very limited ([Wyles, 2015](#)); ([Sulkowski, 2014a](#)). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult-to-treat patients, such as those with cirrhosis.

Last update: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 2 Patients With or Without Compensated Cirrhosis

Recommended regimens listed by evidence level for:

Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis^a


| RECOMMENDED | DURATION | RATING  |
|---|----------|--|
| 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) ^b | 12 weeks | IIb, B |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimen for:

Sofosbuvir + NS5A-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis^a

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

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

Recommended Regimens

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 infection, 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 infection. The single genotype 2-infected 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-naive or -experienced (interferon or peginterferon \pm ribavirin, or sofosbuvir plus ribavirin \pm peginterferon) genotype 2-infected patients without cirrhosis. 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 \pm 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 infection and compensated cirrhosis. Treatment-naive and -experienced patients (interferon or peginterferon \pm ribavirin, or sofosbuvir plus ribavirin \pm 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 infection). The SVR12 in the genotype 2-infected patients was 100% (31/31) ([Forns, 2017](#)).

No sofosbuvir treatment failures were included in the SURVEYOR study, which investigated 8 weeks of therapy in patients with genotype 2 infection without cirrhosis. 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: May 24, 2018

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 \(Including NS5A Inhibitors\), Genotype 3 Patients With or Without Compensated Cirrhosis](#)

Last update: September 21, 2017

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  |
|---|----------|--|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) ^a | 12 weeks | I, A |
| ALTERNATIVE | DURATION | RATING  |
| Daily daclatasvir (60 mg) ^b plus sofosbuvir (400 mg) ^a | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^c | 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 |

^a Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

^b The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on [HIV/HCV coinfection](#) for patients on antiretroviral therapy.

^c This is a 3-tablet coformulation. 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 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin ([Pianko, 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-infected 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 genotype 3-infected patients without cirrhosis.

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 patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) ([Foster, 2015a](#)).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom sofosbuvir/velpatasvir is being considered. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

Alternative Regimens

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-3 study evaluated a 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) in treatment-naïve or -experienced (interferon-based therapy or sofosbuvir plus ribavirin), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Treatment-experienced, genotype 3-infected patients without cirrhosis did well with an SVR12 rate of 94% (32/34) ([Nelson, 2015](#)).

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 patients ([Nelson, 2015](#)). The SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) ([Foster, 2015a](#)).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom daclatasvir plus sofosbuvir is being considered. If the Y93H substitution is identified, a different recommended regimen should be used, or weight-based ribavirin should be added as an alternative option.

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-infected patients without cirrhosis or with compensated cirrhosis. Among the 44 treatment-experienced patients without cirrhosis, the SVR rates were 91% (20/22) and 96% (21/22) for 12 weeks and 16 weeks, respectively. All 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-infected, 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 infection 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 noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis ([Jacobson, 2017](#)). Thus, this regimen

is recommended as an alternative option for patients with genotype 3 infection 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 rate of 84% (21/25) ([Foster, 2015a](#)). Due to the low number of patients with the Y93H mutation in the POLARIS-3 study and the difficult-to-treat nature of treatment-experienced, genotype 3-infected patients, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Last update: September 21, 2017

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^a  | | |
|---|----------|--|
| RECOMMENDED | 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)/voxilaprevir (100 mg) | 12 weeks | IIb, B |
| ALTERNATIVE | DURATION | RATING  |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin | 12 weeks | I, B |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b | 16 weeks | IIa, B |
| ^a For decompensated cirrhosis , please refer to the appropriate section. ^b This is a 3-tablet coformulation. Please refer to the prescribing information. | | |

Recommended 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 for treatment-naïve or -experienced, genotype 3-infected 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/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 infection 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 noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis ([Jacobson, 2017](#)). Thus, this regimen is recommended in patients with genotype 3 infection and cirrhosis.

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 rate of 84% (21/25) ([Foster, 2015a](#)). Patients with genotype 3 infection, prior non-DAA treatment failure, and cirrhosis are among the most difficult to treat. For this reason, ribavirin is recommended for all patients receiving sofosbuvir/velpatasvir, making this an alternative regimen. Due to the low number of patients with the Y93H mutation in the POLARIS-3 study, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Alternative Regimens

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-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis ([Foster, 2015a](#)). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. Among those with both compensated cirrhosis and prior treatment, the SVR12 rate was 89% (33/37). The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin ([Pianko, 2015](#)).



In the POLARIS-3 study noted previously, the SVR12 rate in the 32 patients with prior peginterferon/ribavirin treatment failure and cirrhosis was 91% (29/32). Although the 2 virologic failures did not have Y93H at baseline, both developed treatment-emergent Y93H mutations ([Jacobson, 2017](#)). Based on this finding and analogous to the similar ALLY-3 study, the addition of weight-based ribavirin (if not contraindicated) is recommended for all treatment-experienced, genotype 3-infected patients with compensated cirrhosis when using sofosbuvir/velpatasvir pending additional data. Due to the need for ribavirin, this is recommended as an alternative regimen.

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-infected patients without cirrhosis or with compensated cirrhosis. Among the 47 treatment-experienced participants with compensated cirrhosis who were treated for 16 weeks, the SVR rate was 96% (45/47). One of the virologic failures was a relapse and the other was 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](#)).

Last update: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis

| Recommended regimen for: | | |
|---|----------|--|
| DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis ^a  | | |
| 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, weight-based ribavirin is recommended. | 12 weeks | Ila, C |
| ^a For decompensated cirrhosis , please refer to the appropriate section. | | |

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir ± Ribavirin

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 3 infection, 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 infection) or 12 weeks of sofosbuvir/velpatasvir (52 with genotype 3 infection). SVR rates for the genotype 3-infected 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](#)).

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 infection) versus placebo. The SVR12 rate was 95% (74/78) for the genotype 3-infected 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. However, in NS5A inhibitor-experienced genotype 3-infected patients with cirrhosis, the relapse rate is higher and adding weight-based ribavirin is recommended to minimize relapse risk.

Last update: September 21, 2017



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 \(Including NS5A Inhibitors\), Genotype 4 Patients With or Without Compensated Cirrhosis](#)

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

| Recommended and alternative regimens listed by evidence level and alphabetically for: Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis | | |
|---|----------|--|
| 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) ^a | 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 | 12 weeks | IIa, B |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | IIa, B |
| ALTERNATIVE | DURATION | RATING  |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 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 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin | 16 weeks | IIa, B |
| ^a This is a 3-tablet coformulation. Please refer to the prescribing information. | | |

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 infection 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 infection. 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 patients with genotype 2, 4, 5, or 6 infection without cirrhosis. Patients were treatment naïve or experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Forty-six genotype

4-infected 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 is 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-naive (n=66) and -experienced (n=37) patients with genotype 4 infection ([Asselah, 2018c](#)). The overall SVR12 rate among treatment-experienced, genotype 4-infected 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. However, trends emerged 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-infected 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 infection 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 rate of 94% (32/34) in treatment-experienced patients with genotype 4 infection ([Asselah, 2018b](#)).

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was an open-label, phase 2b study that included a cohort of 49 noncirrhotic, treatment-experienced patients (peginterferon/ribavirin) with genotype 4 infection who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. Based on intention-to-treat analysis, SVR12 was achieved in 100% of these patients. The regimen was well tolerated with no serious adverse events reported ([Hézode, 2015](#)).

The phase 3, open-label, partly randomized AGATE-II trial enrolled genotype 4-infected, treatment-naive or -experienced (interferon-based therapy) patients, without cirrhosis or with compensated cirrhosis. The 100 noncirrhotic participants were treated with 12 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 in this group of patients was 94% (94/100) ([Esmat, 2015a](#)).



These data support the use of paritaprevir/ritonavir/ombitasvir plus ribavirin for 12 weeks in treatment-experienced, genotype 4-infected patients. Due to the need for ribavirin resulting in a greater pill burden and adverse events profile, this regimen is an alternative recommendation.

Last update: September 21, 2017

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^a

| 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 | 12 weeks | IIa, B |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b | 12 weeks | IIa, B |
| ALTERNATIVE | DURATION | RATING  |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin ^c | 12 weeks | I, A |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin | 16 weeks | IIa, B |
| Daily ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin | 12 weeks | IIa, B |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.
^b This is a 3-tablet coformulation. Please refer to the prescribing information.
^c Please see statement on FDA [warning](#) regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection 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 infection. 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 infection ([Asselah, 2018c](#)). The overall SVR12 rate among treatment-experienced, genotype 4-infected 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. However, trends emerged 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 nonribavirin-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-infected 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 infection 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 infection (unknown number with prior treatment experience) achieved SVR.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

The AGATE-I trial randomized 120 treatment-naïve or -experienced patients (interferon-based regimens) with genotype 4 infection and compensated cirrhosis to 12 weeks or 16 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated ([Asselah, 2015a](#)).

The phase 3, open-label, partly randomized AGATE-II trial included a cohort of 60 treatment-naïve or -experienced (interferon-based regimens), genotype 4-infected patients with compensated cirrhosis. These participants were randomized to 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rate from the 12-week arm was 97%.

These data support the use of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with compensated cirrhosis ([Esmat, 2015a](#)). Due to the number of treatment options that exist, including those that do not use ribavirin, this is an alternative rather than a recommended option.

Ledipasvir/Sofosbuvir + Ribavirin

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection 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 rate of 94% (32/34) in treatment-experienced patients with genotype 4


infection ([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.

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DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients, With or Without Compensated Cirrhosis

Recommended regimen for:

DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients, With or Without Compensated Cirrhosis^a 

| RECOMMENDED | DURATION | RATING  |
|--|----------|--|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) | 12 weeks | I, A |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 4 infection, with or without compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The trials included 22 genotype 4-infected patients with a prior treatment failure with an NS5A inhibitor-containing DAA regimen, and 19 genotype 4-infected 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 in these patients. Overall, 46% of patients in these clinical trials had compensated cirrhosis, although the number of genotype 4-infected 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](#)).

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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 \(Including NS5A Inhibitors\), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis](#)

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

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

Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis^a **i**

| RECOMMENDED | DURATION | RATING i |
|--|----------|-----------------|
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b for patients without cirrhosis | 8 weeks | Ila, B |
| <hr/> | | |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b for patients with compensated cirrhosis | 12 weeks | I, B |
| Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | Ila, B |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | Ila, B |
| <p>^a For decompensated cirrhosis, please refer to the appropriate section.</p> <p>^b This is a 3-tablet coformulation. Please refer to the prescribing information.</p> | | |

Recommended Regimens

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 1,904 patients participating in phase 2 and phase 3 clinical trials included 30 patients with genotype 5 infection and 41 with genotype 6 infection ([Puoti, 2017](#)). Approximately 21% to 26% of patients in the overall study had a prior interferon-based treatment failure (DAA failure was excluded); no patients had cirrhosis. SVR among treatment-naïve or -experienced, genotype 5-infected participants was 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-infected participants were 90% (9/10) 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 infection. 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 rate was 96% (24/25). The single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events ([Gane, 2015](#)).

Similarly, 41 patients with genotype 5 infection were treated with 12 weeks of ledipasvir/sofosbuvir. The group included both treatment-naive and -experienced patients, with and without cirrhosis. The 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 infection and 41 patients with genotype 6 infection. 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: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Recommended regimen for:

DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis^a 

| RECOMMENDED | DURATION | RATING  |
|--|----------|--|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) | 12 weeks | Ila, B |

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

Recommended Regimen

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 infection with a history of treatment failure with a DAA-containing regimen. All 7 patients with genotype 5 or 6 infection (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: September 21, 2017

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