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

### 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 (100 mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients. Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. There was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure using a non-NS5A inhibitor sofosbuvir-containing DAA regimen.

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

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

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<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for genotype 1a patients</td>
<td>12 weeks</td>
<td>I, A</td>
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<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)*, regardless of subtype</td>
<td>12 weeks</td>
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<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients</td>
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<tr>
<td>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin, except in simeprevir failures</td>
<td>12 weeks</td>
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* Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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Glecaprevir/Pibrentasvir

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

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

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

Sofosbuvir/Velpatasvir

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

Alternative Regimen

Ledipasvir/Sofosbuvir + Ribavirin

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

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Related References


