### Treatment-Naive Genotype 3 With Compensated Cirrhosis

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

<table>
<thead>
<tr>
<th>Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration</th>
<th>Rating</th>
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<tr>
<td><strong>RECOMMENDED</strong></td>
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<tr>
<td>Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 weeks&lt;sup&gt;c&lt;/sup&gt;</td>
<td>I, B</td>
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<tr>
<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H for velpatasvir</td>
<td>12 weeks</td>
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<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS Y93H for velpatasvir</td>
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<td>Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H for velpatasvir</td>
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<td>IIa, B</td>
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**Recommended Regimens**

**Glecaprevir/Pibrentasvir**

SURVEYOR-II—a partially randomized, open-label, multicenter, 4-part, phase 2 trial—compared 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, to glecaprevir/pibrentasvir plus ribavirin among 48 treatment-naive, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 (<sup>Kwo, 2016b</sup>).

A recent real-world cohort of 723 Italian treatment-naive and -experienced patients with or without cirrhosis were treated with glecaprevir/pibrentasvir according to the manufacturer’s prescribing information. One hundred percent (21/21) of patients with genotype 3 infection who received 12 or 16 weeks of glecaprevir/pibrentasvir (likely indicative of more advanced liver disease or treatment experience) achieved SVR12, compared to 95.8% (46/48) who received an 8-week regimen (<sup>D’Ambrosio 2019</sup>). Comparably high SVR12 rates were reported with 12 weeks of glecaprevir/pibrentasvir among cirrhotic persons with genotype 3 infection in other real-world cohorts (<sup>Drysdale, 2019</sup>); (<sup>Sterling, 2019</sup>).

EXPEDITION-8 included an evaluation of glecaprevir/pibrentasvir for a reduced duration of 8 weeks in treatment-naive patients with compensated cirrhosis including genotype 3 (n=63). Patients with a prior history of decompensation,
hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. Among the participants with genotype 3, 95% (60/63) achieved SVR12 with a single participant experiencing virologic failure (relapse) and 2 participants lost to follow-up (Brown, 2019).

### Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 randomized 552 treatment-naive and -experienced patients (without cirrhosis or with compensated cirrhosis) to 12 weeks of sofosbuvir/velpatasvir or 24 weeks sofosbuvir plus ribavirin (Foster, 2015a). Among those with compensated cirrhosis, the SVR12 was 93% (40/43) in the sofosbuvir/velpatasvir arm compared to 73% (33/45) among those in the sofosbuvir plus ribavirin arm. Of the 250 participants who received sofosbuvir/velpatasvir, 16% (n=43) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline substitutions. Eighty-four percent (21/25) of those with Y93H achieved SVR12 compared to 97% (242/249) in those without this RAS (Foster, 2015a). Ribavirin use was not evaluated in this study.

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). The SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR. Four participants in the sofosbuvir/velpatasvir arm had the Y93H substitution; all achieved SVR12.

To explore whether ribavirin is required for patients with genotype 3 infection and cirrhosis, a randomized, open-label study of 204 genotype 3 patients with compensated cirrhosis (including participants with NS3/4 protease inhibitor and NS5B inhibitor treatment experience) was conducted at 29 sites in Spain. SVR12 was achieved in 91% without ribavirin (5% relapse rate) and 96% with ribavirin (2% relapse rate). Baseline NS5A RASs affected response rates. Among patients with Y93H RAS, 50% (2/4) treated with sofosbuvir/velpatasvir without ribavirin achieved SVR12 compared to 89% (8/9) among those receiving ribavirin as part of their treatment regimen (Esteban, 2018). In 293 patients with genotype 3 infection (25% with cirrhosis and 4% with DAA experience) enrolled in a multicenter cohort study from Germany in which patients received 12 weeks of sofosbuvir/velpatasvir with or without ribavirin, there was only 1 virologic failure in a patient with DAA treatment experience (von Felden, 2018). All 5 genotype 3 cirrhotic patients with RASs were prescribed ribavirin along with sofosbuvir/velpatasvir and achieved SVR. Pending further data on optimal therapy in the setting of a baseline Y93H substitution, patients with compensated cirrhosis should have ribavirin added to the regimen of sofosbuvir/velpatasvir or another regimen should be considered.

### Alternative Regimen

#### Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). Thirty-one percent of participants were interferon treatment experienced. The SVR12 rate was 96% in both arms, 106/110 of patients randomized to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir. There were 2
virologic failures in each arm (2 relapses in the sofosbuvir/velpatasvir/voxilaprevir arm; 1 virologic breakthrough and 1 relapse in the sofosbuvir/velpatasvir arm). Baseline RASs had no effect on treatment response. Among the 6 participants with Y93H in the sofosbuvir/velpatasvir/voxilaprevir arm and 4 in the sofosbuvir/velpatasvir arm, all achieved SVR12.

Additionally, no patients receiving sofosbuvir/velpatasvir/voxilaprevir with virologic failure developed RASs. Although an 8-week regimen was studied in POLARIS-3, a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir was approved by the FDA for the indication of retreatment of DAA-experienced patients and could be considered as an alternative regimen for patients with cirrhosis and Y93H.

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Related References


