




## Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: <b>Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis<sup>a</sup></b> 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>b</sup>	8 weeks	I, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS Y93H	12 weeks	IIa, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H	12 weeks	IIa, B
<sup>a</sup> For <a href="#">decompensated cirrhosis</a> , please refer to the appropriate section. <sup>b</sup> Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.		

## Recommended Regimens

### 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-naïve 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-naïve 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. A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 96.9% (314/324) among adults with genotype 3 infection and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

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.

Another recent study provided information about use of sofosbuvir/velpatasvir therapy in patients with genotype 3b infection, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial enrolled patients from Asia (predominantly China) and treated them with 12 weeks of sofosbuvir/velpatasvir. Ninety percent (60/67) of patients with cirrhosis achieved SVR12 ([Wei, 2019](#)). In the subset of 14 patients with genotype 3b infection and cirrhosis, however, only 50% (7/14) achieved SVR12. All patients with genotype 3b enrolled in this trial had NS5A RASs at either A30K or L31M, or both. The influence of subtype and RASs on SVR rates warrants consideration in the use of sofosbuvir/velpatasvir among cirrhotic patients with genotype 3 infection, although genotype 3b is rare in non-Asian populations.

If NS5A resistance testing is unavailable, glecaprevir/pibrentasvir should be used. If drug drug interactions or other considerations preclude the use of glecaprevir/pibrentasvir then a referral to a specialist in HCV treatment should be considered.

## 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-naïve, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 ([Kwo, 2016b](#)).

A recent real-world cohort of 723 Italian treatment-naïve 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 ([D'Ambrosio 2019](#)). Comparably high SVR12 rates were reported with 12 weeks of glecaprevir/pibrentasvir among cirrhotic persons with genotype 3 infection in other real-world cohorts ([Drysdale, 2019](#)); ([Sterling, 2019](#)).

EXPEDITION-8 included an evaluation of glecaprevir/pibrentasvir for a reduced duration of 8 weeks in treatment-naïve 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](#)).

## 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-naïve 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

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