**Recommended Regimens**

**Glecaprevir/Pibrentasvir**

ENDURANCE-2 was a randomized, double-blind, placebo-controlled trial 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 among 302 genotype 2-infected treatment-naive or -experienced participants. Treatment-experienced patients included those previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon. Patients randomized to placebo later received open-label treatment with glecaprevir/pibrentasvir for 12 weeks. Among 202 patients randomized to active treatment, 70% (141/202) were treatment naive and none had cirrhosis. The SVR12 rates were 99% and 100% by intention-to-treat and modified intention-to-treat analysis, respectively. There were no virologic failures. One participant who achieved SVR4 was lost to follow-up before the SVR12 evaluation. There was no effect of baseline RASs on SVR12 rate. Overall, therapy was well tolerated and the adverse event profile was not different compared to placebo (Kowdley, 2016b).

A shorter duration of glecaprevir/pibrentasvir for 8 weeks was evaluated in the SURVEYOR-II, part 4 study. This was a single-arm, phase 2 study that evaluated glecaprevir/pibrentasvir for 8 weeks among 203 treatment-naive or -experienced patients (previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 2, 4, 5, or 6 infection without cirrhosis. Of the 142 genotype 2-infected patients, 137 (96%) were treatment naive. Among the treatment-naive, genotype 2-infected participants, 135/137 (99%) achieved SVR12. The presence of baseline RASs had minimal effect on SVR12 rates. Fifty-three of 126 (42%) treatment-naive and -experienced participants with genotype 2 had the L31M RAS within the NS5A gene at baseline. Fifty-one of 53 (96%) of these participants achieved SVR12 (Hassanein, 2016).

While not a head-to-head comparison, the results of ENDURANCE-2 and SURVEYOR-II, part 4 indicate that glecaprevir/pibrentasvir administered for 8 or 12 weeks is highly efficacious among genotype 2-infected, treatment-naive patients without cirrhosis.
**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 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir (SVR12 99% vs 94%); (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced participants without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in participants with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure.

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (Jacobson, 2017).

**Alternative Regimen**

**Daclatasvir + Sofosbuvir**

A 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC50) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir plus sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir plus sofosbuvir for 12 weeks is reasonable.

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**Related References**


