**Recommended Regimens**

### Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 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 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (222/233 participants receiving the 12-week regimen; 149/157 participants receiving the 8-week regimen) (Foster, 2017). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8- and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared to the standard of care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. While the baseline presence of the Y93H substitution did not affect SVR rates (10/10 with Y93H achieved SVR with an 8 week duration vs 165/171 without Y93H), the presence of the A30K substitution was associated with a lower SVR rate (14/18 with A30K substitution achieved SVR with an 8 week duration vs 161/163 without A30K) (Krishnan, 2018). Of the 14 treatment-naive patients with genotype 3 without cirrhosis with baseline A30K who received a 12 week duration of glecaprevir/pibrentasvir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence to recommend testing for RASs or extension of therapy in the setting of A30K at this time, but the effect of the A30K mutation should continue to be explored in real world cohorts. These data support an 8-week regimen of glecaprevir/pibrentasvir for the treatment of genotype 3-infected patients who are treatment-naive 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 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis (Foster, 2015a). Among treatment-naive, noncirrhotic patients, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared to 90% (141/156) for sofosbuvir plus ribavirin. Among patients with compensated cirrhosis, SVR12 was 93% (40/43) for sofosbuvir/velpatasvir compared to 73% (33/45) for sofosbuvir plus ribavirin. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline RASs. Forty-eight percent (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with cirrhosis.

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in genotype 3-infected, noncirrhotic patients who were either treatment-naive or interferon-experienced. Eighty-nine genotype 3 patients received the sofosbuvir/velpatasvir regimen and 97% achieved SVR12 (86/89) (Jacobson, 2017). There were no virologic failures. This confirms the efficacy of sofosbuvir/velpatasvir in genotype 3-infected patients without cirrhosis.

**Alternative Regimen**

**Daclatasvir + Sofosbuvir**

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. Among treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12; in treatment-naive patients with compensated cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests that patients with genotype 3 infection and compensated cirrhosis are likely to benefit from an extension of therapy.

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% (149/162) in those without it (Nelson, 2015). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with compensated cirrhosis had lower SVR12 rates (1/5); (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

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Related References


