Similar results were observed in the CUPILT cohort of 11 subjects whose HCV infection recurred after liver transplantation, mainly treated for 24 weeks; 10 of these subjects achieved an SVR (Coilly *et al.*, 2015).

Taken together, all these data indicate that the combination of sofosbuvir and daclatasvir is safe and reasonably effective in all patients, whatever the HCV genotype. However, lacking a rigorous clinical trial, that conclusion is tentative.

5b. Sofosbuvir and ledipasvir

Ledipasvir is a NS5A inhibitor with multigenotypic activity but a modest barrier to resistance. The once-daily fixed-dose combination of sofosbuvir plus ledipasvir (marketed as Harvoni by Gilead Sciences) is the first-in-market for the treatment of HCV infection, and it has a good safety profile (Table 262.5). Recent data demonstrated that this combination alone or in combination with ribavirin is able to cure HCV infection in ≥ 90% of patients with genotype 1, 4, 5, and 6. This combination appears to be suboptimal in genotype 3 patients, and using combinations with sofosbuvir, and either daclatasvir or velpatasvir, will help fill this gap now and in the near future.

GENOTYPE 1

Summary of pivotal studies

The efficacy and safety of the 12-week Harvoni regimen was evaluated in several clinical trials involving > 2000 genotype 1, treatment-naive patients and > 1800 treatment-experienced patients. The overall efficacy was excellent, with SVR rates > 95% in both treatment-naive and -experienced patients.

Treatment-naive patients

The initial phase II studies (ELECTRON and LONESTAR) showed that an ultra-short duration of treatment for 6 weeks was suboptimal in genotype 1, treatment-naive patients, whereas 8- or 12-week regimens appeared to be optimal (Gane *et al.*, 2013a; Lawitz *et al.*, 2014a).

Three large phase III trials were conducted to clarify the optimal treatment duration of the sofosbuvir–ledipasvir combination and the need for ribavirin. In the ION-1 study, 865 genotype 1, treatment-naive patients were randomized to receive Harvoni with or without ribavirin for 12 or 24 weeks (Afdhal *et al.,* 2014b). The SVR rate in this study was ≥ 97% regardless of whether the regimen was given for 12 or 24 weeks and whether it included ribavirin. It is not surprising that the rates of treatment discontinuation were higher those treated for 24 weeks than in those treated for 12 weeks; similarly, the rates of side effects were higher in the groups that received ribavirin than those that did not. Moreover, SVR rates were uniform regardless of patients' pretherapy characteristics, and the 136 subjects with cirrhosis still had excellent SVR rates (97–100%). All patients had a good safety profile. The ION-1 study showed that 12 weeks of sofosbuvir–ledipasvir is highly effective in genotype 1, treatment-naive patients without additional benefit gained from extending treatment duration or adding ribavirin. These results were confirmed in a Japanese phase III trial with 97% genotype 1b patients who were treated with sofosbuvir–ledipasvir without or with ribavirin for 12 weeks. SVR results were 100% and 96%, respectively, confirming that addition of ribavirin is unnecessary in this population (Mizokami *et al.*, 2015).

In the ION-3 study, 647 treatment-naive genotype1 patients without cirrhosis were randomized to receive ledipasvir–sofosbuvir regimen with or without ribavirin for 8 weeks or the same regimen for 12 weeks (Kowdley *et al.*, 2014). The rates of SVR in the three treatment groups were high, > 90% (93% for the fixed-dose combination [FDC] for 8 weeks, 94% FDC plus ribavirin for 8 weeks, and 95% FDC for 12 weeks). The results of noninferiority analysis suggested that adding ribavirin to the 8-week FDC regimen or extending duration from 8 to 12 weeks did not result in improved SVR rates. SVR rates were uniform regardless of the baseline characteristics historically associated with a poor response to PR. Although relapse was more common among patients who received 8 weeks of treatment (20 vs. 3; 4.6% vs. 1%), no baseline characteristics or on-treatment variables could be identified associated with relapse. It is interesting that the relapse rates were 1% (1/84) and 1% (1/96) in female patients treated for 8 weeks with FDC without and with ribavirin, respectively, and 8% (10/129) and 7% (8/114) in males respectively. *Post hoc* analysis indicated that only treatment-naive noncirrhotic patients with an HCV RNA level < 6 million IU/ml (6.8 log) at baseline could be treated for 8 weeks. However, the HCV RNA level determination can be different according to the currently available assays. Therefore external confirmation was needed.

The ledipasvir–sofosbuvir combination regimen was also evaluated in HIV–HCV genotype 1 co-infected patients. In a phase II study (ERADICATE), this combination was given without ribavirin for 12 weeks in 50 patients, 13 not treated for their HIV infection and 37 receiving antiretroviral therapy. All but 1 patient (98%) achieved an SVR (Townsend *et al.*, 2014). In the ION-4 phase III study, 150 treatment-naive co-infected patients receive ledipasvir–sofosbuvir without ribavirin for 12 weeks, with 95% achieving an SVR (Naggie *et al.*, 2015).

Treatment-experienced patients

The ION-2 study looked at the outcomes of sofosbuvir–ledipasvir treatment of HCV-infected, genotype 1 patients (79% genotype 1a) who had previously failed therapy with PR with or without telaprevir or boceprevir (Afdhal *et al.*, 2014a). The subjects were randomized to 12 or 24 weeks of therapy, with subrandomization to yes or no to ribavirin. The SVR rates in this study were similar to ION-1, with widely overlapping confidence intervals for SVR rates, regardless of treatment duration or use of ribavirin. However, this study was not powered to compare responses to regimens with or without ribavirin or to 12 or 24 weeks of treatment. There was no difference in SVR between patients who previously failed either PR or triple therapy, PR plus first-generation protease inhibitors (PIs). In cirrhotic patients, SVR rates