**Table 1.1** Clinical results in a Phase 2a study of daclatasvir (**1**) combined with PEG-IFN/RBV.

| *Assessments*[a] | *Placebo (n = 12)*[b] | *3 mg (n = 12)* | *10 mg (n = 12)* | *60 mg (n = 12)* |
|---|---|---|---|---|
| RVR | 1 (8%) | 5 (42%) | 11 (92%) | 10 (83%) |
| eRVR | 1 (8%) | 5 (42%) | 10 (83%) | 9 (75%) |
| cEVR | 5 (42%) | 7 (58%) | 10 (83%) | 10 (83%) |
| $SVR_{12}$ | 3 (25%) | 5 (42%) | 11 (92%) | 10 (83%) |
| $SVR_{24}$ | 3 (25%) | 5 (42%) | 10 (83%) | 10 (83%) |
| Virological failure | 9 (75%) | 7 (58%) | 2 (17%) | 2 (17%) |

[a]RVR, viral RNA undetectable at 4 weeks; eRVR, viral RNA undetectable at both 4 and 12 weeks; cEVR, RNA undetectable at 12 weeks; $SVR_x$, sustained virological response at $x$ weeks after end of therapy.
[b]Treated with PEG-IFN/RBV.

and 24 weeks after the end of the dosing period ($SVR_{12}$ and $SVR_{24}$). The results of this trial are compiled in Table 1.1 and indicate that the two higher doses of **1** are associated with greater efficacy, with 5 of 12 (42%) patients in the 3 mg group achieving eRVR compared with 10 of 12 (83%) and 9 of 12 (75%) of those receiving 10 and 60 mg of drug, respectively, whereas only 1 of the 12 (8%) administered with just PEG-IFN/RBV achieved this endpoint.[76] Based on results from subsequent Phase 2b trials, the 60 mg dose of **1** was selected for Phase 3 studies.

The first step towards a PEG-IFN/ribavirin-free therapy was a short clinical trial in which 74 treatment-naive and null-responding HCV-infected patients – the latter are the most difficult to treat patient subgroup – were administered a combination of the HCV NS3 protease inhibitor danoprevir (**46**) at doses of 100 or 200 mg tid or 600 or 900 mg bid and the nucleoside prodrug mericitabine (**47**) at doses of 500 or 1000 mg bid, for up to 13 days against a placebo control arm ($n = 14$) (Figure 1.12).[77] In the treated subjects who completed the 13 days of therapy, the viral load declined by a median 3.7–5.2 $\log_{10}$ IU $mL^{-1}$, which compared with an increase of 0.1 $\log_{10}$ IU $mL^{-1}$ observed in the placebo arm.

A more recent clinical trial examined the potential of a combination of daclatasvir (**1**) (60 mg qd) and the NS3 protease inhibitor asunaprevir (**48**) (600 mg bid) to cure a small cohort of G-1-infected null responders who were administered the drugs for 24 weeks with and without PEG-IFN/RBV (**49**).[78,79] In this trial, all 10 patients administered the quadruple drug regimen experienced $SVR_{12}$ and 9 of the 10 maintained this status to 24 weeks post-dosing, while the remaining patient had detectable HCV RNA at week 24 after cessation of drug but had undetectable viral RNA 35 days later. Nine of the 10 patients had an SVR at 48 weeks, with the remaining patient having measurable RNA at less than 25 IU $mL^{-1}$ at week 48, but undetectable 13 days later. The cohort receiving only the combination of the two DAAs comprised nine G-1a and two G-1b infections. Of these, two G-1b- and two G-1a-infected subjects experienced an SVR at 12 and 24 weeks after drug therapy was completed and three of these maintained SVR at week 48, while the fourth one had detectable