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HCV protease inhibitor telaprevir: phase II clinical results

Chronic hepatitis C virus (HCV) infection is the leading cause of both cirrhosis and hepatocellular carcinoma. It is estimated that worldwide approximately 180 million people are chronically infected with HCV. Current treatment for HCV genotype-1, the most common genotype, consists of a 48-week course of peginterferon combined with ribavirin resulting in a sustained virologic response (defined as undetectable HCV RNA levels 24 weeks after cessation of treatment) in approximately 40–50% of patients. Because of this inadequate response rate, there is a strong medical need for new drugs to treat chronic HCV infection. Results from two phase II trials of the Vertex's orally bioavailable first-in-class HCV nonstructural 3/4A (NS3/4A) protease inhibitor telaprevir (**1**, Fig. 1), have recently been reported [1,2].

The first trial (PROVE1) examined the addition of telaprevir to standard of care treatment, peginterferon alfa-2a (180 μg per week) and ribavirin (1000 or 1200 mg QD, according to body weight). Patients were assigned to one of the four different groups differing by the length of treatment with telaprevir [1]. One group (75 patients) received placebo while the other groups received telaprevir (1250 mg on day 1) followed by 750 mg TID for 12 weeks, 24 weeks or 48 weeks. In the placebo group, a sustained virologic response was obtained in 41% of patients (31 of 75 patients). For the telaprevir groups, the sustained virologic response rate was 35% (6 of 17 patients) for the 12-week group, 61% (48 of 79 patients) for the 24-week group, and 67% (53 of 79 patients) for the 48-week group. Discontinuation because of adverse events was higher in the telaprevir groups than in the control group (21% for the telaprevir groups versus 11% for the control group) and the most common adverse event was rash. Overall, telaprevir significantly increased the rate of response when added to the current standard of care.

The second trial (PROVE2) examined treatment with telaprevir and peginteferon alfa-2a with or without ribavirin. Patients were assigned to one of four different groups based on different combinations of the three agents [2]. The control group received peginterferon alfa-2a 180 μg per week and ribavirin (according to body weight) for 48 weeks. The second group of patients was treated with telaprevir (1250 mg on day 1 and 750 mg every 8 h thereafter) and peginterferon for 12 weeks followed by 12-week treatment with telaprevir, peginterferon and ribavirin. The third group was treated with telaprevir and peginterferon for 12 weeks while the final group was treated with telaprevir, peginterferon and ribavirin for 12 weeks. The highest response rate (69%) was seen in the second group where ribavirin was present in the past 12 weeks of a 24-week regimen. In the 12-week treatment groups (groups three and four), there was a higher response rate (60%) when ribavirin was included compared to treatment with telaprevir and peginterferon alone (36% response rate). Overall, telaprevir once again significantly increased the rate of response when added to the current standard of care treatment. However, the study also demonstrated the ribavirin remains integral to obtaining a sustained virologic response compared to treatments where it is not included.

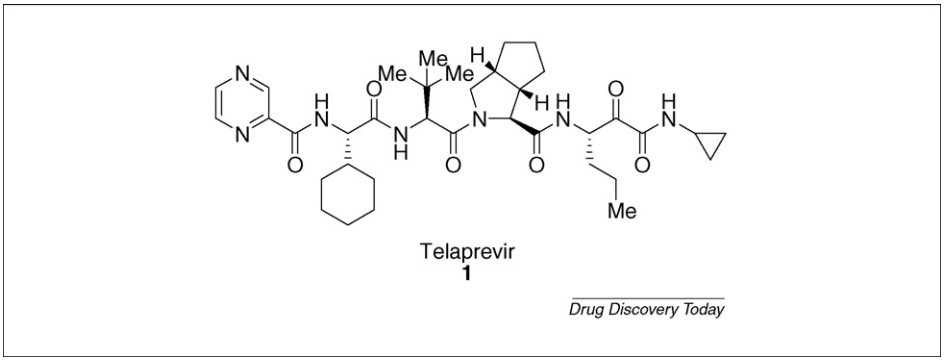

FIGURE 1
Structure of telaprevir **1**.

1 McHutchison, J.G. *et al.* (2009) Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N. Engl. J. Med.* 360, 1827–1838
2 McHutchison, J.G. *et al.* (2009) Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N. Engl. J. Med.* 360, 1839–1850

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