Debio 025 is the first oral non-structural protease inhibitor with clinically confirmed Anti-HCV properties.1,2 Debio 025 is currently in phase II clinical development and results to date are promising since patient survival both in vitro and in vivo have been demonstrated.

In preliminary studies in replicon models, Debio 025 displayed high antiviral potency towards wild-type and HCV replicons resistant to NS3 protease and NS5B polymerase inhibitors.3,4 Results of phase I clinical trials in HCV/HIV-coinfected patients revealed both anti-HBV and anti-HCV activity of Debio 025 monotherapy.5 In the phase II study that followed (study DEB-025-HCV-203), combination therapy with Debio 025 and peg-IFN-alpha 2b was shown to be generally well tolerated and resulted in an additive antiviral effect in genotype 1, 4, and 6-coinfected patients.6 Transient hyperbilirubinemia was observed in some patients treated with peg-IFN-alpha 2b, but no hepatitis was reported with a higher than anticipated Debio 025 dose. So, far, no signs of viral breakthrough or emergence of resistance have been reported in phase II and III studies.7

The aim of this follow-up study was to assess the antiviral efficacy of protease-inhibitor peg-IFN2a (peg-IFN2a) and ribavirin (RBV) in patients with chronic hepatitis C who received standard care (SOC) therapy after completion of 4 weeks of experimental medication with Debio 025 with or without peg-IFN2a followed by 3 weeks of follow-up (study DEB-025-HCV-203).

Materials and Methods

In the initial randomised, double-blind, placebo-controlled, escalating-dose-ranging phase II study, the short-term antiviral efficacy of oral Debio 025 with or without peg-IFN2a was assessed in treatment-naive HCV-mono-infected male or female patients with compensated liver function. Patients were randomised to 5 treatment arms receiving peg-IFN2a (200,000 IU w/ or w/o Debio 025) combined with 200, 600 or 1000 mg Debio 025 or placebo, or 1000 mg Debio 025 monotherapy. Within treatment arms, patients were stratified by genotype (12 patients infected with genotype 1 or 4, and 6 patients with genotype 2 or 3). Debio 025 was administered for 28 days in 2 dose levels twice daily for one week, followed by once daily for three weeks. A final study assessment was performed 21 days after treatment end (+ Day 50), and this time point was defined as the baseline for the follow up study presented below.

This was an observational follow up study of patients with chronic hepatitis C previously treated in the phase II study outlined above.

Follow up study endpoints comprised:

• Sustained viral response (SVR) rate defined as undetectable HCV RNA at week 24 after SOC treatment discontinuation (primary endpoint).
• Proportion of patients with normal ALT at week 24 after SOC treatment discontinuation.
• Incidence of adverse events during SOC treatment.

Patients received SOC treatment at a dose and for a duration adapted to their genotype, i.e. genotype 3 patients (GT3) received peg-IFN2a 180µg/week + RBV 800 mg/day for 24 weeks after SOC treatment end and genotype 1 or 4 patients (GT1/4) received peg-IFN2a 180µg/week + RBV 1000/1200 mg/day for 48 weeks. Efficacy was assessed at the end of SOC treatment and 24 weeks later.

At the end of Debio 025 treatment the initial study, 6 out of 20 GT1A patients (30%) had undetectable HCV RNA levels. Five patients (25%) still had undetectable levels at the start of SOC treatment for the follow up study 3 weeks later. Twenty-four weeks after SOC therapy end, the number of patients with undetectable HCV RNA rose to 15 (65%). End of treatment response and post-treatment response were difficult to assess because of the high rate of missing values (55%) at the end of the 48-week treatment (Fig 1).

Six out of 6 GT3 patients (67%) had undetectable HCV RNA levels at the end of Debio 025 treatmnet in the initial study. This figure was the same at the start of SOC treatment for the follow up study and rose to 8 out of 9 (89%) at the end of SOC treatment. Interpretation of the SVR rate (87%) is based on the absence of results in 2 patients (22%) (Fig 2).

The number of patients with elevated ALT levels at the start of Debio 025 treatment in the initial study was 25 (86%). This population decreased to only 1 (2 missing values) at the end of treatment with Debio 025. Interpretation of the results during and after SOC treatment in the follow up study was biased by the high number of missing values, but since only 1 patient had elevated ALT during and after treatment, it seems that the positive effect on ALT induced by treatment with Debio 025 (with or without peg-IFN2a) was maintained during follow up treatment with SOC (Figure 3).

Conclusion

Follow on SOC treatment after initial treatment with peg-IFN2a and/or Debio 025 was well tolerated without signs of adverse events than could be traced back to Debio 025 treatment.

Initial evolution in viral loads obtained under Debio 025 treatment were maintained in GT3 patients residing in SVR in 6 out of 7 patients who complete follow up data were available. In GT1 patients, follow on treatment with SOC resulted in an increase in the number of patients with undetectable HCV RNA. Thirteen out of 18 patients for whom follow up data are available achieved SVR.

References