Research Article

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STARTVerso1: A randomized trial of faldaprevir plus pegylated interferon/ribavirin for chronic HCV genotype-1 infection☆

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Background & Aims: The efficacy and tolerability of faldaprevir, a potent hepatitis C virus (HCV) NS3/4A protease inhibitor, plus peginterferon (PegIFN) and ribavirin (RBV) was assessed in a double-blind, placebo-controlled phase 3 study of treatment-naïve patients with HCV genotype-1 infection.

Methods: Patients were randomly assigned (1:2:2) to PegIFN/RBV plus: placebo (arm 1, n = 132) for 24 weeks; faldaprevir (120 mg, once daily) for 12 or 24 weeks (arm 2, n = 259); or faldaprevir (240 mg, once daily) for 12 weeks (arm 3, n = 261). In arms 2 and 3, patients with early treatment success (HCV-RNA <25 IU/ml at week 4 and undetectable at week 8) stopped all treatment at week 24. Other patients received PegIFN/RBV until week 48 unless they met futility criteria. The primary endpoint was sustained virologic response 12 weeks post-treatment (SVR12).

Results: SVR12 was achieved by 52%, 79%, and 80% of patients in arms 1, 2, and 3, respectively (estimated difference for arms 2 and 3 *vs.* arm 1: 27%, 95% confidence interval 17%–36%; and 29%, 95% confidence interval, 19%–38%, respectively; p <0.0001 for both). Early treatment success was achieved by 87% (arm 2) and 89% (arm 3) of patients, of whom 86% and 89% achieved SVR12. Adverse event rates were similar among groups; few adverse events led to discontinuation of all regimen components.

Conclusions: Faldaprevir plus PegIFN/RBV significantly increased SVR12, compared with PegIFN/RBV, in treatment-naïve patients with HCV genotype-1 infection. No differences were seen in responses of patients given faldaprevir once daily at 120 or 240 mg.

Keywords: NS3/4A protease inhibitor; SVR12; Early treatment success; DAA; Clinical trial; Phase 3.

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Abbreviations: HCV, hepatitis C virus; PI, protease inhibitor; PegIFN, peginterferon; RBV, ribavirin; SVR, sustained virologic response; DDI, drug–drug interaction; BID, twice daily; ETS, early treatment success; TD, target detected; TND, target not detected; EVR, early virologic response; ETR, end of treatment response; RVR, rapid virologic response; cEVR, complete early virologic response; PPV, positive predictive value; NPV, negative predictive value; AE, adverse event; DAIDS, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; ITT, intention-to-treat; RAV, resistance-associated variant; GI, gastrointestinal; ULN, upper limit of normal.

Introduction

The introduction of the hepatitis C virus (HCV) NS3/4A protease inhibitors (PI) telaprevir and boceprevir represented a major advance in the treatment of chronic HCV genotype-1. Telaprevir or boceprevir with peginterferon (PegIFN) and ribavirin (RBV) resulted in a sustained virologic response (SVR) in 63%–75% of treatment-naïve patients, compared with 38%–44% with PegIFN and RBV alone [1–4]. However, these drugs have limitations, including serious skin reactions with telaprevir [5], and an increased incidence of anemia, compared with PegIFN and RBV alone, with both telaprevir and boceprevir [1–4]. Furthermore, both drugs also display a wide range of drug–drug interactions (DDIs), have a high pill burden, and require twice daily (BID) or three times daily dosing [5–9].

Faldaprevir (BI 201335) is a potent HCV NS3/4A PI administered once daily [10–12]. Four phase 2 studies evaluated the efficacy and safety of faldaprevir with PegIFN alfa-2a plus RBV [13–16]. In genotype-1 treatment-naïve patients, SVR rates of up to 84% were achieved compared with 56% for placebo plus PegIFN and RBV [13]. In addition, SVR rates were similar with faldaprevir 120 mg for 12 or 24 weeks [16]. The addition of faldaprevir to PegIFN and RBV was not associated with an increased incidence of anemia compared with PegIFN and RBV alone [13,16] and there have been no reports of potentially life-threatening cutaneous adverse reactions in phase 2 studies [13,14,16]. Studies of faldaprevir and antiretrovirals have shown a lower potential for DDIs than first-wave PIs [17].

STARTVerso1 was a phase 3 study designed to assess the efficacy and safety of faldaprevir with PegIFN and RBV in treatment-naïve patients with chronic HCV genotype-1 infection.

Patients and methods

Patients

Patients were recruited from nine European countries and Japan. Eligible patients were treatment-naïve, aged 18–70 years (Europe), or 20–70 years (Japan), with chronic HCV genotype-1 infection diagnosed by positive anti-HCV antibodies and HCV RNA ⩾1000 IU/ml at screening plus a positive antibody or HCV RNA test more than 6 months before screening, or a liver biopsy consistent with chronic HCV infection.

Patients with compensated liver disease, including cirrhosis, were eligible for inclusion. All patients had a liver biopsy within 3 years or had a FibroScan® within 6 months of randomization to determine fibrosis stage. For patients without a liver biopsy, fibrosis stage was determined by FibroScan® results using a cut-off value of 9.5 kPa to indicate fibrosis stage ⩾F3 (<9.5 kPa F0–F2; ⩾9.5 kPa F3–F4), consistent with evaluations of the use of FibroScan® in chronic HCV [18,19]; however, there are no reliable cut-offs in the literature for distinguishing <F3 from ⩾F3. The FibroScan® threshold for cirrhosis was ⩾13 kPa, based on the results of a meta-analysis by Friedrich-Rust *et al.*, and consistent with results of other studies [20,21]. Main exclusion criteria included mixed-genotype HCV; HIV or hepatitis B co-infection; decompensated liver disease; and contraindications to PegIFN or RBV. Asian patients were limited to 20% of the total population.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 study (Fig. 1). Patients were randomized 1:2:2 to arm 1, 2, or 3. Patients in arm 1 received placebo plus PegIFN and RBV for 24 weeks, then PegIFN and RBV for 24 weeks. Patients in arm 2 received faldaprevir 120 mg once daily plus PegIFN and RBV. Those with early treatment success (ETS, HCV RNA <25 IU/ml target detected [TD] or target not detected [TND] at week 4 and <25 IU/ml TND at week 8) stopped faldaprevir at week 12 and received placebo plus PegIFN and RBV for a further 12 weeks. Patients without ETS received faldaprevir plus PegIFN and RBV for 24 weeks, then PegIFN and RBV for a further 24 weeks. In arm 3, all patients received faldaprevir 240 mg once daily plus PegIFN and RBV for 12 weeks followed by placebo plus PegIFN and RBV to week 24, and either stopped treatment (ETS) or continued PegIFN and RBV to week 48 (no ETS) (Fig. 1). A single loading dose of faldaprevir was administered on day 1 (arm 2 = 240 mg; arm 3 = 480 mg). All study medication was stopped in the event of virologic breakthrough at or after week 4 (increase in HCV RNA ⩾1 $\log_{10}$ from nadir or ⩾25 IU/ml after an initial decrease to <25 IU/ml), lack of early virologic response (EVR; decrease in HCV RNA ⩾2 $\log_{10}$ from baseline at week 12), or lack of virologic response (detectable HCV RNA at week 24).

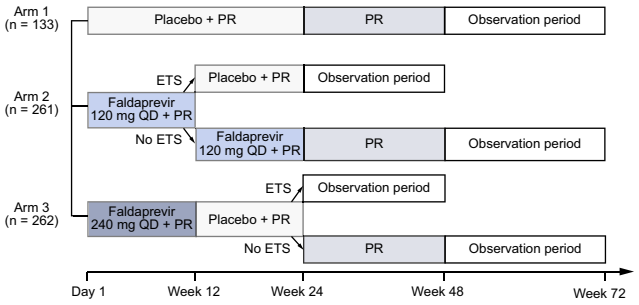

Fig. 1. STARTVerso1 study design. ETS, early treatment success (HCV RNA <25 IU/ml at week 4 and target not detected at week 8); PR, PegIFN alfa-2a and RBV.

PegIFN (alfa-2a) was administered subcutaneously at 180 μg once weekly. RBV was administered orally at a total dose of 1000 or 1200 mg (for bodyweight <75 kg or ⩾75 kg, respectively) daily in two divided doses, except in Japan where the total dose was 600, 800, or 1200 mg (for bodyweight ⩽60 kg, >60–⩽80 kg, or >80 kg, respectively) daily in two divided doses according to the local label. Both faldaprevir and RBV were given with food, a requirement of RBV but not faldaprevir administration. Dose reductions were permitted for PegIFN and RBV, and brief dose interruptions were permitted for all three drugs, but only if medically necessary and following discussion with the clinical monitor. Faldaprevir monotherapy was not permitted. Treatment compliance was monitored using pill counts and syringe counts at each visit.

Concomitant use of the following drugs was not permitted: immunomodulators (including chronic use of systemic corticosteroids); systemic antiviral agents (except for treatment of mild, localized, recurrent herpes simplex, or influenza); and medications that could cause phototoxicity (except RBV). Concomitant treatment with methadone or buprenorphine was excluded, and the use of substrates of P-glycoprotein, UGT1A1, CYP3A4, or CYP2C9 with a narrow therapeutic window were discouraged.

Study documentation, including protocol amendments, was approved by the appropriate institutional review board and the study was carried out in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines. All patients provided written informed consent. An independent data monitoring committee reviewed the efficacy and safety data at regular intervals. All authors had access to the study data and reviewed and approved the final manuscript.

Randomization and blinding

Randomization was carried out using an interactive voice response system, and was stratified according to race (Black, Asian, other) and HCV genotype (genotype-1a, genotype-1b, other). Investigators, sponsor, and patients were blinded to treatment group allocation through the use of matching placebo capsules. HCV RNA results were blinded up to week 8.

Virologic endpoints

The primary endpoint was SVR (HCV RNA <25 IU/ml TND) 12 weeks after completion of therapy (SVR12). Secondary endpoints were ETS, and ALT and AST normalization. Other endpoints were rapid virologic response (RVR, HCV RNA <25 IU/ml TD or TND at week 4); complete EVR (cEVR, HCV RNA <25 IU/ml TND at week 12); and end of treatment response (ETR, HCV RNA <25 IU/ml TND at end of treatment).