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Faldaprevir Combined With Peginterferon Alfa-2a and Ribavirin in Chronic Hepatitis C Virus Genotype-1 Patients With Prior Nonresponse: SILEN-C2 Trial

Mark S. Sulkowski,[1] Marc Bourlière,[2] Jean-Pierre Bronowicki,[3] Tarik Asselah,[4] Jean-Michel Pawlotsky,[5] Stephen D. Shafran,[6] Stanislas Pol,[7] Stefan Mauss,[8] Dominique Larrey,[9] Yakov Datsenko,[10] Jerry O. Stern,[11] George Kukolj,[12] Joseph Scherer,[11] Gerhard Nehmiz,[10] Gerhard G. Steinmann,[10] and Wulf O. Böcher[13]

Faldaprevir (BI 201335) is a potent, hepatitis C virus (HCV) NS3/4A protease inhibitor. In all, 290 noncirrhotic HCV genotype (GT)-1 patients with prior null (<1 $\log_{10}$ viral load [VL] drop at any time on treatment) or partial response (≥1 $\log_{10}$ VL drop but never undetectable on treatment) were randomized 2:1:1 to receive 48 weeks of peginterferon alfa-2a and ribavirin (PegIFN/RBV) in combination with faldaprevir 240 mg once daily (QD) with 3 days PegIFN/RBV lead-in (LI), 240 mg QD without LI, or 240 mg twice daily (BID) with LI. Patients in the 240 mg QD/LI group achieving maintained rapid virologic response (mRVR; VL <25 IU/mL [Roche TaqMan] at week 4 and undetectable at weeks 8 to 20) were rerandomized to cease all treatment at week 24 or continue PegIFN/RBV up to week 48. Sustained virologic response (SVR) rates were 32%, 50%, and 42% in prior partial responders, and 21%, 35%, and 29% in prior null responders in the faldaprevir 240 mg QD/LI, 240 mg QD, and 240 mg BID/LI groups, respectively. In the 240 mg QD/LI group, a significantly higher proportion of mRVR patients rerandomized to 48 weeks' treatment achieved SVR compared with those assigned to 24 weeks treatment (72% versus 43%; $P = 0.035$). Rates of gastrointestinal disorders, jaundice, dry skin, and photosensitivity were increased at 240 mg BID compared with the 240 mg QD dose. Faldaprevir discontinuations owing to adverse events occurred in 6%, 4%, and 23% of patients in the 240 mg QD/LI, 240 mg QD, and 240 mg BID/LI groups, respectively. *Conclusion*: Faldaprevir 240 mg QD with PegIFN/RBV was safe and tolerable and produced substantial SVR rates in prior null and partial responders. The 240 mg QD dose is currently undergoing phase 3 evaluation. (HEPATOLOGY 2013;57:2155-2163)

Hepatitis C represents one of the most common chronic infectious diseases, affecting 150 to 170 million people worldwide. Of the described hepatitis C virus (HCV) genotypes (GT), GT-1 is most common in many parts of the world. Historically, GT-1 has been less responsive to peginterferon alfa (PegIFN) and ribavirin (RBV) treatment, with around 50% to 60% of treatment-naïve patients failing to achieve a sustained virologic response (SVR). Treatment options for these patients were previously limited to a repeated course of PegIFN/RBV, with a low chance of cure (~15% SVR).[1,2] Recent approval of the HCV NS3/4A protease inhibitors (PIs) boceprevir and telaprevir has resulted in significantly improved SVR rates in GT-1-infected patients including those who failed to respond to prior

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice-daily; EoTR, end of treatment response; GT, genotype; HCV, hepatitis C virus; LI, lead-in; LLOD, lower limit of detection; LLOQ, lower limit of quantification; mRVR, maintained rapid virologic response; PegIFN, peginterferon alfa; PI, protease inhibitor; QD, once-daily; RBV, ribavirin; RGT, response-guided therapy; SVR, sustained virologic response; ULN, upper limit of normal; VL, viral load.

From the [1]Viral Hepatitis Center, John Hopkins University School of Medicine, Baltimore, MD, USA; [2]Hôpital Saint Joseph, Marseille, France; [3]INSERM U954, Centre Hospitalier Universitaire de Nancy, Université de Lorraine, Vandoeuvre les Nancy, France; [4]Hôpital Beaujon and INSERM UMR773, Université Denis Diderot Paris 7, France; [5]Hôpital Henri Mondor, University of Paris-Est, and INSERM U955, Créteil, France; [6]University of Alberta, Edmonton, AB, Canada; [7]Université Paris Descartes, INSERM. U1016, APHP Hôpital Cochin, AP-HP, Paris, France; [8]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; [9]Liver Unit and INSERM 1040-IRB, Hôpital Saint-Eloi, Montpellier Cedex, France; [10]Boehringer Ingelheim Pharma, Biberach, Germany; [11]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; [12]Boehringer Ingelheim Laval, Canada; [13]Boehringer Ingelheim Pharma, Ingelheim, Germany.

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PegIFN/RBV treatment.[3,4] However, both agents add significant side effects to those of PegIFN/RBV, including severe skin rashes/pruritus (telaprevir), anal and digestive discomfort (telaprevir), anemia (telaprevir and boceprevir), nausea (telaprevir and boceprevir), and dysgeusia (boceprevir), are dosed thrice-daily, and carry a high pill burden.

Faldaprevir (BI 201335) is a peptidomimetic linear PI which has a long half-life, as demonstrated by preclinical and human pharmacokinetic studies, allowing once-daily (QD) dosing.[5] In phase 1b studies, faldaprevir combined with PegIFN/RBV demonstrated strong antiviral responses and was well tolerated in treatment-naïve and treatment-experienced HCV GT-1 patients.[6] In a phase 2b study of faldaprevir (SILEN-C1), up to 84% of treatment-naïve GT-1 patients achieved SVR and the safety and tolerability profile of faldaprevir was found to be favorable.[7] Moreover, up to 87% of patients achieved the criterion of a maintained rapid virologic response (mRVR; HCV RNA <25 IU/mL at week 4 and undetectable from week 8 to week 20) and qualified for shortened treatment duration with 24 weeks of overall treatment. Here we report the results of a phase 2b multicenter, randomized, double-blind study of faldaprevir in combination with PegIFN/RBV in HCV GT-1-infected patients with nonresponse to prior PegIFN/RBV (SILEN-C2; Safety and antIviraL Effect of faldaprevir iN hepatitis C).

Patients and Methods

Patients

Patients were enrolled at 73 centers in 14 countries (Australia, Austria, Canada, Czech Republic, France, Germany, Republic of Korea, The Netherlands, Portugal, Romania, Spain, Switzerland, United Kingdom, and United States). Eligible patients were 18 to 65 years of age, had chronic HCV GT-1 infection, had previously received at least 12 weeks of combination treatment with an approved dose of PegIFN alfa-2a or alfa-2b combined with RBV, and had detectable HCV RNA at the end of previous treatment. At the time that the protocol was developed and approved, there was no standard definition of null or partial response. Accordingly, virologic failure was defined as either a <1 $\log_{10}$ maximum reduction in HCV RNA at any time during treatment (null response), or a maximal reduction in HCV RNA at any timepoint ≥ 1 $\log_{10}$ but never having achieved HCV RNA below the level of detection (partial response). Relapsers, who experienced undetectable HCV RNA during and/or at the end of prior HCV treatment followed by viral rebound, were specifically excluded from the trial. Other key inclusion criteria included an HCV viral load (VL) of $\geq$100,000 IU/mL at screening and a liver biopsy within 24 months prior to enrollment; patients with histologic cirrhosis were excluded. Patients with evidence of other liver disease, HCV of mixed GT, hepatitis B virus, human immunodeficiency virus, decompensated liver disease, contraindication to PegIFN or RBV, or hyperbilirubinemia ($>1.5 \times$ upper limit of normal [ULN]) were excluded; patients with Gilbert's polymorphism were accepted. Due to the potential for drug interactions, concomitant treatment with medications that are substrates of P-gp, UGT1A1, CYP3A4 or 2C9, with a narrow therapeutic range, were excluded. All patients provided written informed consent prior to trial participation. The study protocol was reviewed and approved by the appropriate Institutional Ethics Committees and health authorities.

Study Design

This was a phase 2b, multicenter, randomized, double-blind trial (NCT00774397). Eligible treatment-experienced patients were randomized to one of three treatment groups in a 2:1:1 ratio: 240 mg faldaprevir QD combined with PegIFN alfa-2a and RBV for 24 weeks, starting with a 3-day lead-in (LI) phase of placebo plus

Address reprint requests to: Mark S. Sulkowski, M.D., Viral Hepatitis Center, Johns Hopkins University School of Medicine, 600 North Wolfe St., 1830 Bldg., Rm. 445, Baltimore, MD 21287. E-mail: msulkowski@jhmi.edu; fax: 410-583-2654.

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Potential conflict of interest: Dr. Sulkowski advises and received grants from Abbott, Boehringer Ingleheim, Bristol-Myers Squibb, Janssen, Merck, Roche, and Vertex. He advises Gilead, Novartis, and Pfizer. Dr. Bronowicki consults for Boehringer Ingleheim. Dr. Asselah consults for, advises, received grants from, and is on the speakers' bureau for Boehringer Ingleheim. Dr. Pawlotsky advises and received grants from Gilead and Roche. He also advises Abbott, Achillion, Anadys, Biotica, Boehringer Ingleheim, Bristol-Myers Squibb, Janssen-Cilag, Madaus-Rottapharm, Merck, and Novartis. Dr. Shafran advises and received grants from Merck, Pfizer, Roche, Abbott, Bristol-Myers Squibb, Gilead, and Vertex. He received grants from Boehringer Ingleheim and GSK. He advises Janssen. Dr. Pol received grants from and is on the speakers' bureau for Bristol-Myers Squibb, Boehringer Ingleheim, Gilead, Novartis, MSD, and Janssen. Dr. Mauss advises and is on the speakers' bureau for Boehringer Ingleheim and Roche. Dr. Larrey consults, received grants from, and is on the speakers' bureau for Roche. He consults for and received grants from Boehringer Ingleheim, Bristol-Myers Squibb, and Gilead. He consults and is on the speakers' bureau for Merck. He received grants from Abbott.

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PegIFN/RBV, and followed by an additional 24 weeks of PegIFN/RBV (240 mg QD/LI); 240 mg faldaprevir QD combined with PegIFN alfa-2a and RBV for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV (240 mg QD); 240 mg faldaprevir twice daily (BID) combined with PegIFN alfa-2a and RBV for 24 weeks, starting with a 3-day LI phase of placebo plus PegIFN/RBV, and followed by an additional 24 weeks of PegIFN/RBV (240 mg BID/LI). The rationale for the 3-day LI phase was that short delay of the first intake of faldaprevir would allow sufficient levels of PegIFN and RBV to be achieved prior to the administration of faldaprevir to prevent the possibility of functional faldaprevir monotherapy. Three days was thought to be sufficient based on the observation that the antiviral effect of interferon can be observed within 1 to 2 days of dosing.[8] For all patients, a loading dose of 480 mg faldaprevir was administered on the morning of the first day of faldaprevir treatment. In the 240 mg QD/LI treatment group, all patients achieving mRVR, defined as HCV VL below the lower limit of quantification (LLOQ) at week 4 (HCV RNA <25 IU/mL) and undetectable from week 8 to week 20 (HCV RNA <17 IU/mL), were rerandomized at week 24, at a ratio of 1:1, to either continue PegIFN/RBV up to week 48 or stop all treatment at week 24. PegIFN alfa-2a was administered subcutaneously at a dose of 180 μg per week, and RBV was given orally at a dose of 1,000 mg/day (body weight <75 kg) or 1,200 mg/day (body weight ≥75 kg) in two divided doses. Faldaprevir and RBV were administered with food. Hematopoietic growth factors were not provided but allowed at the discretion of the investigator for the management of anemia and neutropenia. Stopping criteria for virologic failure were as follows: HCV VL rebound by ≥1,000 IU/mL after previous VL below the lower limit of detection (LLOD), in two consecutive visits at least 2 weeks apart; lack of early virologic response, defined as an absence of drop by ≥2 $\log_{10}$ from baseline VL at week 12; or absence of VL below the LLOD at week 24. There were no protocol-specified laboratory or clinical stopping rules for bilirubin elevations.

Efficacy Assessments

Efficacy Endpoints. The primary efficacy endpoint of the study was SVR, defined as HCV RNA below the LLOD 24 weeks after the end of all anti-HCV therapy. Secondary efficacy endpoints included mRVR (defined in the study design section) and the occurrence of rebound, in particular breakthrough and relapse. End of treatment response (EoTR) was defined as HCV RNA not detected at end of treatment. Rebound was defined as HCV RNA >1 $\log_{10}$ from nadir, or ≥100 IU/mL after previous VL below the LLOD in two consecutive visits at least 2 weeks apart. Breakthrough was defined as HCV RNA rebound during faldaprevir/placebo treatment or subsequent PegIFN/RBV treatment. Relapse was defined as HCV RNA undetectable at the end of treatment but detectable during the follow-up period. Nonresponse was used to define patients who did not achieve SVR, but did not experience a virologic breakthrough or relapse.

Analysis of Plasma HCV RNA and GT. Plasma HCV RNA levels were measured using the Roche COBAS TaqMan HCV/HPS (v. 2.0) assay at a central laboratory, with an LLOQ of 25 IU/mL and an LLOD of 17 IU/mL. HCV GT for screening and randomization was determined using the Trugene HCV assay (Bayer, Leverkusen, Germany); due to the technical limitations of this genotyping assay,[9] definitive HCV GTs and subtypes used for all analyses were based on complete NS3/4A sequencing and phylogenetic analyses for all randomized patients.

Genotypic and Phenotypic Resistance Monitoring. Samples for genotyping the HCV NS3/4A protease were collected at all patient visits. Retrospective viral genotyping was performed for all patients at baseline, for patients who discontinued study treatment due to virologic failure or who had VL plateaus above the LLOQ, or VL rebounds during or after the end of treatment. Viral RNA was isolated from plasma using the QiaAmp Viral RNA extraction kit. cDNA was synthesized using Superscript III one-step reverse transcription polymerase chain reaction system with platinum Taq DNA polymerase using GT-specific primers. The length of amplified product potentially limits the detection to samples with VL $>10^3$ IU/mL. The NS3/4A protease nucleotide sequence was obtained by direct DNA sequencing of the amplified product using Big Dye Terminator V3.1 and the ABI 3130x1 Genetic Analyzer (Applied Biosystems) detection system that allows for the detection of variants present at ≥30%.

Safety Assessments

A written record of all adverse events (AEs), including time of onset, end time, and intensity of the event, as well as any treatment or action required for the event and its outcome, was kept by each investigator. All AEs, including rash, were graded based on tolerability until the introduction of a rash management plan, defined as follows: mild (localized), moderate (diffuse, 30% to <70% body surface area), or severe (diffuse generalized, >70% body surface area or mucous membrane involvement or organ dysfunction or signs of anaphylaxis or life threatening). The intensity of all

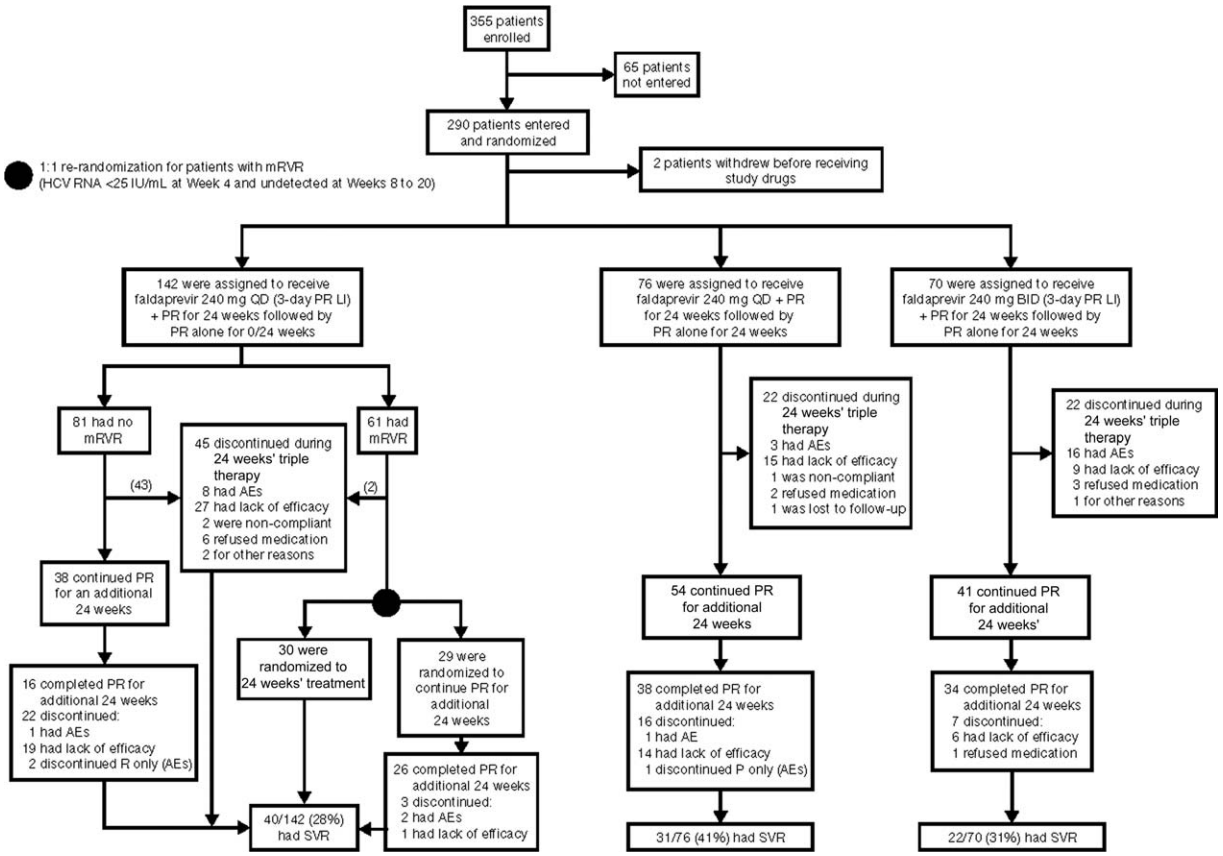

Fig. 1. Patient flow diagram. P, R PegIFN/RBV.

other AEs was judged based on a patient's tolerability of the event as being mild (easy to tolerate), moderate (interference with usual activity), or severe (incapacitating or causing inability to work or to perform usual activities). Vital signs and electrocardiograms were also evaluated, as were routine laboratory parameters.

Statistical Assessments

Descriptive statistics for efficacy and safety endpoints were reported. All *P*-values reported are 2-sided and were calculated using Fisher's exact test. All efficacy and safety results relate to all treated patients (Fig. 1). The sample size in this phase 2 trial was based on an optimization approach for the probability of correctly selecting the most efficacious dose for phase 3.

Results

Patient Disposition and Baseline Characteristics. Of 355 patients enrolled in the trial, 290 patients were randomized to treatment (Fig. 1). Of these, 288 patients received at least one dose of treatment; 192 patients completed treatment with faldaprevir, while 96 patients prematurely discontinued for reasons including AEs (n = 27), lack of efficacy (n = 51), refusal to continue the study medication (n = 11), noncompliance with the protocol (n = 3), and other reasons (n = 4) including one patient lost to follow-up. Following completion of the faldaprevir dosing phase, PegIFN/RBV was continued in 162 patients and completed in 114 patients, while 30 were rerandomized to stop all therapy (Fig. 1).

Baseline characteristics were similar among the three treatment groups (Table 1); 67% of patients were male, mean age was 49 years, 5% of patients were black (Hispanic patients were classed as white), and mean $\log_{10}$ HCV RNA was 6.58 IU/mL. As expected for prior nonresponders, only 4% of patients (among those with available IL28B GT data) had the CC polymorphism (rs12979860) (Table 1). Among all patients, 51% were infected with GT-1a and 47% with GT-1b. The majority of patients were documented null responders (47%; using stringent criteria of <1 $\log_{10}$ reduction in HCV RNA at any time during previous treatment) or prior partial responders (36%) to previous treatment (Table 1).

Efficacy. Overall, SVR was achieved by 28% of patients in the 240 mg QD/LI group, 41% in the 240 mg QD group, and 31% in the 240 mg BID/LI group (Fig. 2A). Compared with patients with prior

Table 1. Summary of Baseline Characteristics

	Faldaprevir 240 mg QD/LI (n = 142)	Faldaprevir 240 mg QD (n = 76)	Faldaprevir 240 mg BID/LI (n = 70)	Total (n = 288)
Gender, n (%)				
Male	101 (71)	50 (66)	41 (59)	192 (67)
Female	41 (29)	26 (34)	29 (41)	96 (33)
Ethnicity, n (%)				
Asian	6 (4)	5 (7)	2 (3)	13 (5)
Black	5 (4)	7 (9)	3 (4)	15 (5)
White	131 (92)	64 (84)	65 (93)	260 (90)
Age, years				
Mean	49	50	50	49
Standard deviation	9.6	8.4	8.3	9.0
HCV RNA, $\log_{10}$ IU/ml				
Mean	6.60	6.56	6.55	6.58
Standard deviation	0.45	0.43	0.49	0.46
GT, n (%)				
1	1 (1)	0	1 (1)	2 (1)
1a	78 (55)	42 (55)	27 (39)	147 (51)
1b	61 (43)	33 (43)	42 (60)	136 (47)
Other GT-1	2 (1)	1 (1)	0	3 (1)
IL28B genotype (rs12979860), n (%)				
CC	5 (4)	2 (3)	4 (6)	11 (4)
Non-CC	56 (39)	30 (39)	32 (47)	118 (41)
Missing	81 (57)	44 (58)	34 (46)	159 (55)
Previous response to treatment, n (%)				
Null responder	57 (40)	40 (53)	38 (54)	135 (47)
Partial responder	54 (38)	26 (34)	24 (34)	104 (36)
Null or partial responder*	13 (9)	3 (4)	5 (7)	21 (7)
Breakthrough	2 (1)	0	0	2 (1)
Prior efficacy not assessable†	16 (11)	7 (9)	3 (4)	26 (9)

*The category 'null or partial responder' was used by investigators for confirmed non-responders with insufficient data to categorize them as null or partial responders.

†The category 'prior efficacy not assessable' includes patients who discontinued previous treatment between 12 and 24 weeks of treatment and had detectable HCV RNA at the end of treatment. Patients discontinued for various reasons.

null response, the rate of SVR was higher in patients with prior partial response (Fig. 2B), as expected. SVR was achieved by 32%, 50%, and 42% of prior partial responders in the 240 mg QD/LI, 240 mg QD, and 240 mg BID/LI treatment groups, respectively; corresponding rates in prior null responders were 21%, 35%, and 29%. SVR rates among patients infected with GT-1a tended to be lower than among patients infected with GT-1b virus.

Protocol-defined mRVR was achieved by 43%, 45%, and 47% of patients in the 240 mg QD/LI, 240 mg QD, and 240 mg BID/LI treatment groups, respectively (Fig. 2A). In the 240 mg QD/LI group, 59 patients who achieved mRVR were rerandomized to complete 24 or 48 weeks of PegIFN/RBV (total duration); the rate of SVR was significantly higher in patients treated for 48 weeks (72%) compared with those treated for 24 weeks (43%; $P = 0.035$) and virologic relapse was significantly lower in patients treated for 48 weeks (21%) compared with those treated for 24 weeks (57%; $P = 0.0073$) (Fig. 2C). Relapse occurred in 27% of patients with 240 mg QD/LI, 12% of patients with 240 mg QD, and 20% of patients with 240 mg BID/LI. The higher relapse rate in the 240 mg QD/LI group was mainly driven by frequent relapses in patients who obtained mRVR and were rerandomized to shortened treatment duration.

Breakthrough was observed in 24% of patients on faldaprevir treatment, with GT-1a viruses largely encoding NS3 R155 mutants and GT-1b viruses encoding only D168 changes (Table 2). The median time for faldaprevir breakthrough was 30 days (range 14 to 169). Of note, the viral breakthrough rate was lower in patients treated with 240 mg BID/LI (17%) and substitutions at position 155 were not observed in patients infected with GT-1a. After discontinuation of faldaprevir, virologic breakthrough during PegIFN/RBV therapy occurred in 6% of patients and was mainly associated with R155K mutations. Other nonresponse and relapse within all faldaprevir treatment arms was observed in 33% of patients and was characterized by R155K (37/51) substitutions for GT-1a virus and D168V (23/43) changes for GT-1b. However, in these groups 23%

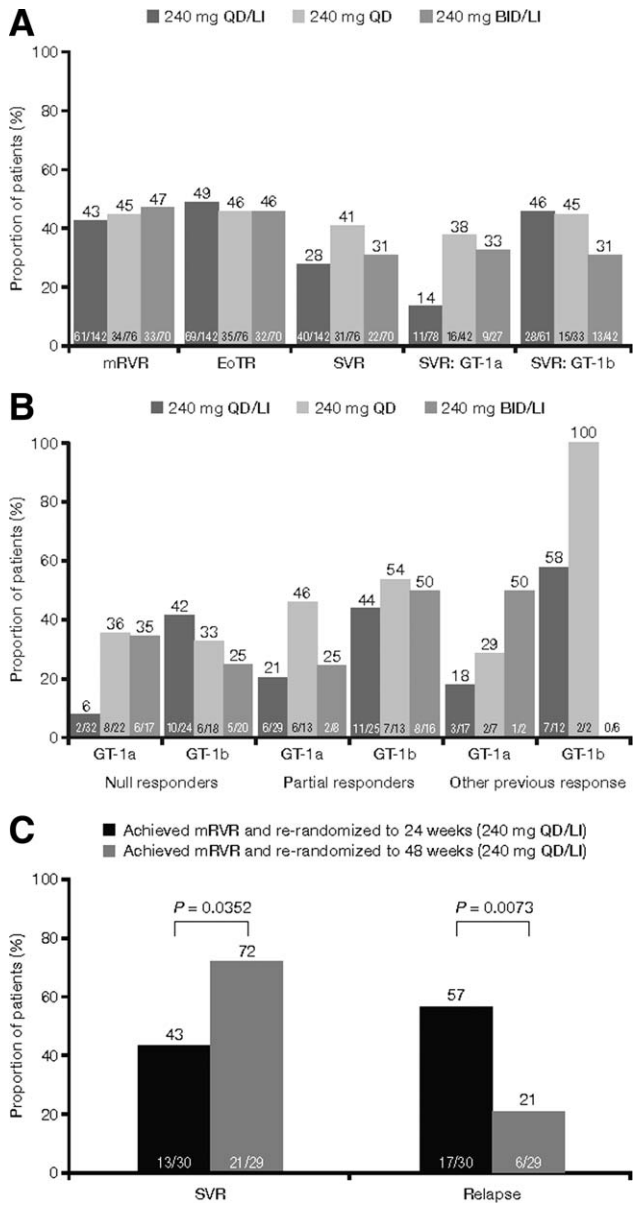

Fig. 2. Frequency of patients with (A) overall virologic response, (B) SVR by prior nonresponse and GT, and (C) SVR/relapse by prior nonresponse according to rerandomization to 24 or 48 weeks of PegIFN/RBV following achievement of mRVR (240 mg QD/LI group only; other groups did not have rerandomization among patients who achieved mRVR).

(22/94) had viruses that lacked known resistant mutations.

Safety. The most frequent AEs were those typical of PegIFN/RBV treatment, and in most cases were mild or moderate in intensity. Table 3 lists the most common AEs reported at an incidence of >20% in any group during the 24 weeks of treatment with faldaprevir or placebo and PegIFN/RBV. Based on prior studies, gastrointestinal disorders (nausea, diarrhea, and vomiting), skin events (rash and photosensitivity), and jaundice associated with elevated unconjugated bilirubin levels were considered to be potentially related to faldaprevir; these events were frequently observed during the initial weeks of therapy (Table 3). The rates of gastrointestinal disorders, jaundice, dry skin, and photosensitivity were higher in the 240 mg BID group compared with the 240 mg QD dose groups, suggestive of a dose-response relationship.

Serious AEs were more common in patients in the 240 mg BID/LI group (19%) compared with those in the 240 mg QD/LI and 240 mg QD groups (7% in both groups) and included anemia (4%, 1%, and 0%, respectively), gastrointestinal disorders (6%, 1%, and 0%, respectively), and skin and subcutaneous tissue

Table 2. Response to Faldaprevir and PegIFN/RBV Per Treatment Group

	Patients with Virologic Response, n (%)		
	Faldaprevir 240 mg QD/LI (n = 142)	Faldaprevir 240 mg QD (n = 76)	Faldaprevir 240 mg BID/LI (n = 70)
SVR	40 (28)	31 (41)	22 (31)
Missing SVR	5 (4)	4 (5)	5 (7)
HCV RNA never undetectable	16 (11)	5 (7)	12 (17)
Breakthrough during faldaprevir*	36 (25)	22 (29)	12 (17)
Breakthrough during PegIFN/RBV*	7 (5)	5 (7)	5 (7)
Relapse	38 (27)†	9 (12)	14 (20)

*Breakthrough in patients with nadir HCV RNA <LLOD.

†The relapse rate in the faldaprevir 240 mg QD/LI group presented here includes all patients in the group, including those who achieved mRVR and were re-randomized to 24 weeks' total treatment duration. These patients had a higher relapse rate than those who achieved 48 weeks' total treatment duration, so comparisons of the relapse rates between the treatment groups should be made with caution.

Table 3. Most Frequent AEs (>20% Frequency in Any Treatment Group)

	Most Frequent Adverse Events, n (%)		
	Faldaprevir 240 mg QD/LI (n = 142)	Faldaprevir 240 mg QD (n = 76)	Faldaprevir 240 mg BID/LI (n = 70)
Nausea	68 (48)	40 (53)	44 (64)
Headache	56 (40)	32 (42)	31 (45)
Pruritus	43 (30)	34 (45)	23 (33)
Fatigue	49 (35)	30 (39)	25 (36)
Diarrhea	45 (32)	24 (32)	27 (39)
Jaundice	25 (18)	10 (13)	26 (38)
Influenza-like illness	45 (32)	21 (28)	23 (33)
Vomiting	24 (17)	17 (22)	22 (32)
Rash	35 (25)	14 (18)	21 (30)
Asthenia	34 (24)	15 (20)	20 (29)
Dry skin	26 (18)	13 (17)	20 (29)
Photosensitivity reaction	19 (13)	10 (13)	20 (29)
Myalgia	24 (17)	17 (22)	17 (25)
Decreased appetite	28 (20)	14 (18)	16 (23)
Pyrexia	26 (18)	12 (16)	16 (23)
Anemia	10 (7)	10 (13)	16 (23)
Insomnia	30 (21)	12 (16)	14 (20)

Table 4. Safety Laboratory Parameters During Treatment With Faldaprevir and PegIFN/RBV

n (%)	Faldaprevir 240 mg QD/LI (n = 141)	Faldaprevir 240 mg QD (n = 76)	Faldaprevir 240 mg BID/LI (n = 70)
Total bilirubin (0.1 to 1 mg/dL)			
≤1.0 x ULN	3 (2)	2 (3)	1 (1)
>1.0 to 1.5 x ULN	19 (13)	15 (20)	0
>1.5 to 2.5 x ULN	45 (32)	22 (29)	8 (11)
>2.5 to 5 x ULN	60 (43)	27 (36)	37 (53)
>5 x ULN	14* (10)	10† (13)	24‡ (34)
ALT (0 to 56 U/L)			
≤1.25 x ULN	37 (26)	16 (21)	12 (17)
>1.25 to 2.5 x ULN	66 (47)	40 (53)	34 (49)
>2.5 to 5 x ULN	32 (23)	15 (20)	22 (31)
>5 to 10 x ULN	6 (4)	5 (7)	1 (1)
>10 x ULN	0	0	1 (1)
Hemoglobin (12.5 to 18 g/dL)			
≥10 g/dL	128 (91)	64 (84)	55 (79)
8.5 to <10 g/dL	9 (6)	10 (13)	10 (14)
7.5 to <8.5 g/dL	3 (2)	1 (1)	2 (3)
6.5 to <7.5 g/dL	1 (1)	0	2 (3)
<6.5 g/dL	0	1 (1)	1 (1)
Absolute neutrophil count (1960 to 7230/μL)			
≥1300/μL	61 (43)	34 (45)	38§ (54)
1000 to <1300/μL	33 (23)	9 (12)	17 (24)
750 to <1000/μL	31 (22)	11 (14)	12 (17)
500 to <750/μL	11 (8)	18 (24)	2 (3)
<500/μL	5 (4)	4 (5)	1 (1)

*Three patients reached values >10 x ULN, the maximum was 12.6 x ULN, with direct/total ratio = 0.4/12.6 = 0.032; all others remained <10 x ULN.

†One patient reached 11.2 x ULN, with direct/total ratio = 0.6/11.2 = 0.054; all others remained <10 x ULN.

‡Two patient reached values >10 x ULN, the maximum was 11.2 x ULN, with direct/total ratio = 0.9/11.2 = 0.080; all others remained <10 x ULN.

§One patient stopped treatment after 3-day LI phase.

disorders (7%, 0%, and 3%, respectively). No deaths were observed. Discontinuations due to AEs were rather frequent in the 240 mg BID/LI group (23%) but low with the 240 mg QD/LI group (6%) and the 240 mg QD group (4%). AEs leading to discontinuation were mainly rash (10%, 0%, and 0%, respectively), asthenia (4%, 0%, and 0%, respectively), nausea (3%, 1%, and 0%, respectively), vomiting (4%, 1%, and 1%, respectively), increased bilirubin (3%, 1%, and 0%, respectively), and jaundice (1%, 1%, and 0%, respectively). Some patients had more than one AE at the time of discontinuation.

Changes in laboratory values were generally consistent with those commonly reported for PegIFN/RBV. Decreases in hemoglobin, platelets, and white blood cell count were observed at frequencies similar to those observed with PegIFN/RBV and descriptive analysis did not reveal any clinically relevant differences between dose groups (no statistical analyses were conducted; Table 4).[10] Erythropoietin was received by 6% to 14% of patients (two patients received transfusions; one in the 240 mg QD arm and one in the 240 mg BID/LI arm). Increases in total bilirubin, characterized by predominance of the unconjugated (indirect) fraction, were common during faldaprevir therapy and rapidly returned to pretreatment levels in all patients after faldaprevir was discontinued. Elevations in bilirubin were not associated with increases in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, or other markers of liver injury (Supporting Table 1).

Discussion

Treatment with the PI, faldaprevir 240 mg QD, in combination with PegIFN and RBV, led to virologic cure (SVR) in ~35% and 50% of HCV GT-1 patients with strictly defined prior null or partial response to PegIFN/RBV. Interestingly, higher SVR rates were not observed in patients treated with 3-day LI of PegIFN/RBV compared with those treated with all three drugs simultaneously from the start. While 240 mg BID/LI was associated with lower rates of virologic breakthrough, the SVR rate achieved with this regimen was lower than the rate achieved with 240 mg QD, largely due to higher rates of treatment discontinuation due to AEs.

This trial excluded patients with liver cirrhosis and used a more stringent definition of null (<1 $\log_{10}$ reduction in HCV RNA at any time during previous treatment) and partial response (≥1 $\log_{10}$ reduction in VL but never undetectable on treatment) than clinical trials with other HCV PIs plus PegIFN/RBV in treatment-experienced patients.[3,4,11] The manner in which prior HCV treatment response was collected in this study did not permit retrospective analysis of the current definitions of null (<2 $\log_{10}$ reduction in HCV RNA at week 12) and partial response (≥2 $\log_{10}$ reduction in HCV RNA at week 12 but with detectable HCV RNA at week 24). Accordingly, cross-study comparison of these data with other published studies is not possible.[12] A phase 3 trial of faldaprevir plus PegIFN/RBV in treatment-experienced patients classified according to current definitions of null and partial response is ongoing. Prior relapsers are also being assessed in the phase 3 study. While these data are not yet available, this study suggests that, similar to other HCV PIs, prior PegIFN/RBV treatment response impacts the likelihood of response to retreatment with faldaprevir plus PegIFN/RBV.

For telaprevir and boceprevir, shortened response-guided therapy (RGT) provided to patients with rapid virologic response is the standard approach for treatment-naïve patients and prior relapsers (telaprevir). In the US, prior partial responders with RVR are eligible for shortened therapy with boceprevir regimens (but this is not included in the EU label); however, RGT has not been assessed in prior null responders. In this study, virologic relapse occurred in ~60% of prior partial and null responders treated with 240 mg QD/LI who achieved mRVR, and were randomly assigned to stop treatment after 24 weeks. Although it is possible that RGT may have been more effective in patients treated with faldaprevir 240 mg QD without the PegIFN/RBV 3-day LI, we believe that these data provide convincing evidence that RGT should not be considered in this difficult-to-cure patient population. Thus, this concept was abandoned for previous null and partial responders in the ongoing phase 3 clinical trial program.

Importantly, even with longer PegIFN/RBV therapy, SVR rates were lower in patients with prior null response compared with those with prior partial response. In addition, the rate of virologic failure with HCV variants resistant to faldaprevir was higher in null responders, likely reflecting the inability of PegIFN/RBV to eradicate variants with decreased susceptibility to faldaprevir. This finding is consistent with those in clinical trials of boceprevir and telaprevir.[3,4] However, some differences in patterns of resistant variants detected in patients failing faldaprevir were observed compared with those previously reported in patients who failed to respond to telaprevir and boceprevir. Most cases of breakthrough and relapse were due to selection of the well-described resistance mutations R155K (GT-1a) and D168V (GT-1b). Interestingly, a lower breakthrough rate was observed (17%, 12/70) with 240 mg BID/LI, where both GT-1a and GT-1b breakthrough virus encoded D168 mutants exclusively, indicating that the sensitivity shifts of R155K mutants might partially be covered by the increased faldaprevir exposure at this dose level; however, overall efficacy was offset by a higher discontinuation rate in the BID dose group. Wild-type sequence without detectable resistant mutants was found in 23% of nonresponders other than breakthrough (relapsers, other non-SVR) across all arms.

HCV PIs are known to rapidly select for resistant variants when administered as monotherapy.[6,13] Based on the rationale that a short delay in the first intake of a PI may prevent the possibility of functional monotherapy, the effect of a 3-day PegIFN/RBV LI period before initiation of faldaprevir therapy was assessed for the 240 mg QD dose. Consistent with phase 2 results reported in treatment-naïve patients,[7], administration of a 3-day LI with PegIFN/RBV prior to faldaprevir treatment resulted in SVR rates around 10% lower than when the same dose of faldaprevir and PegIFN/RBV were initiated simultaneously. This observation remained valid after sensitivity analysis, which involved the removal of the 30 patients with mRVR who were rerandomized to what was found to be a suboptimal treatment duration (24 weeks). The finding that initiation of PegIFN/RBV prior to HCV PI had a negative effect was unexpected. Interestingly, in two randomized controlled trials (one with boceprevir; one with telaprevir), addition of HCV PI after 4 weeks of PegIFN/RBV therapy (LI) was not associated with a decrease or increase in the proportion of patients achieving SVR. The underlying mechanism for impaired viral response with the 3-day LI in our study is not known; further investigation is ongoing. Given the observed negative effect of 3-day PegIFN/RBV LI, simultaneous start of faldaprevir and PegIFN/RBV will be incorporated into current and future studies of this agent.

Faldaprevir was well tolerated at the 240 mg QD dose. At this dose, the main faldaprevir-related AEs were mild-to-moderate skin rash, photosensitivity reactions, and gastrointestinal events, which tended to occur during the first weeks after faldaprevir initiation up to week 12. Only 6% and 4% of patients discontinued faldaprevir due to AEs in the 240 mg QD/LI and 240 mg QD treatment groups, respectively. However, a much higher rate of discontinuation due to AEs was observed with the 240 mg BID dose (23%) without improved efficacy; thus, this dose will not be investigated in phase 3 studies.

Faldaprevir is associated with incidences of jaundice related to increases in unconjugated bilirubin. Similar to some other HCV PIs in development,[14] faldaprevir-mediated inhibition of normal bilirubin uptake (OATP-1), processing (UGT1A1), and elimination (MRP-2) appear to drive this event.[15] Jaundice was rapidly reversible after cessation of faldaprevir and was not associated with increases in serum ALT, AST, or other markers of liver injury; only three patients discontinued the trial due to jaundice and indirect bilirubin elevation. Skin rash in the 240 mg QD dose groups was mainly mild to moderate and managed without treatment modifications in most instances. In the 240 mg QD dose groups, only one patient discontinued treatment due to rash; however, 10 patients discontinued treatment with the 240 mg BID dose because of rash.

In conclusion, addition of 240 mg QD faldaprevir for 24 weeks to 48-week PegIFN/RBV therapy was

safe and tolerable and produced SVR rates of up to 50% in even the hardest-to-cure patients, i.e., GT-1 patients with null or partial response to prior PegIFN/RBV. Phase 3 trials testing 120 mg and 240 mg QD faldaprevir without LI, in combination with PegIFN/RBV, for treatment-naïve patients and patients with prior treatment failure are ongoing.

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