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Faldaprevir Combined With Pegylated Interferon Alfa-2a and Ribavirin in Treatment-Naïve Patients With Chronic Genotype1 HCV: SILEN-C1 Trial

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Faldaprevir (BI 201335) is a potent, hepatitis C virus (HCV) NS3/4A protease inhibitor with pharmacokinetic properties supportive of once-daily (QD) dosing. Four hundred and twenty-nine HCV genotype (GT)-1 treatment-naïve patients without cirrhosis were randomized 1:1:2:2 to receive 24 weeks of pegylated interferon alfa-2a and ribavirin (PegIFN/RBV) in combination with placebo, faldaprevir 120 mg QD with 3 days of PegIFN/RBV lead-in (LI), 240 mg QD with LI, or 240 mg QD without LI, followed by an additional 24 weeks of PegIFN/RBV. Patients in the 240 mg QD groups achieving maintained rapid virologic response (mRVR; viral load [VL] <25 IU/mL at week 4 and undetectable at weeks 8-20) were rerandomized to cease all treatment at week 24 or continue receiving PegIFN/RBV up to week 48. VL was measured by Roche TaqMan. Sustained virologic response (SVR) rates were 56%, 72%, 72%, and 84% in the placebo, faldaprevir 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD groups. Ninety-two percent of mRVR patients treated with faldaprevir 240 mg QD achieved SVR, irrespective of PegIFN/RBV treatment duration. Eighty-two percent of GT-1a patients who received faldaprevir 240 mg QD achieved SVR versus 47% with placebo. Mild gastrointestinal disorders, jaundice resulting from isolated unconjugated hyperbilirubinemia, and rash or photosensitivity were more common in the active groups than with placebo. Discontinuations resulting from adverse events occurred in 4%, 11%, and 5% of patients treated with 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD of faldaprevir versus 1% with placebo. *Conclusion:* Faldaprevir QD with PegIFN/RBV achieved consistently high SVR rates with acceptable tolerability and safety at all dose levels. The 120 and 240 mg QD doses are currently undergoing phase 3 evaluation. (HEPATOLOGY 2013;57:2143-2154)

Treatment of hepatitis C infection has advanced since its initial characterization.[1] Hepatitis C virus (HCV) genotype (GT)-1 represents the most common GT in many parts of the world and, historically, has been less responsive to peginterferon alfa-2A (PegIFN) and ribavirin (RBV), compared with other HCV GTs, despite longer treatment duration (48 weeks) and higher-dose RBV. Since the proof-of-concept study with the HCV NS3/4A peptidomimetic protease inhibitor (PI), BILN 2061,[2] multiple PIs have entered clinical development. Two PIs, the α-ketoamide derivatives boceprevir and

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; DRESS, drug rash with eosinophilia and systemic symptoms; EVR, early virologic response; GGT, gamma-glutamyl transferase; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IVRS, interactive voice response system; LI, lead-in; LLOD, lower limit of detection; LLOQ, lower limit of quantification; mRVR, maintained rapid virologic response; OR, odds ratio; PCR, polymerase chain reaction; PegIFN, pegylated interferon alfa-2a; PI, protease inhibitor; PK, pharmacokinetic; PR, peginterferon/ribavirin; QD, once-daily; RBV, ribavirin; RGT, response-guided therapy; SJS, Stevens-Johnson syndrome; SVR, sustained virologic response; UGT, uridine diphosphate glucuronosyltransferase; ULN, upper limit of normal; VL, viral load; VR, virologic response.

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telaprevir, have been approved for treatment in many regions of the world. Taken three times daily in combination with PegIFN/RBV, both boceprevir and telaprevir have significantly improved sustained virologic response (SVR) rates and shortened treatment duration in approximately half of treated HCV GT-1 patients, as compared with PegIFN/RBV alone.[3-6] However, both agents carry a high pill burden and add significant side effects to those of PegIFN/RBV, including severe skin rashes/pruritus (telaprevir), anal discomfort (telaprevir), dysgeusia (boceprevir), and anemia (telaprevir and boceprevir).

Faldaprevir is a potent, once-daily (QD), HCV NS3/4A PI[7] with antiviral activity in *in vitro* HCV subgenomic replicon assays, as well as NS3 protease assays derived from HCV GT-1, -4, -5, and -6.[8] Preclinical and human pharmacokinetic (PK) studies suggested that faldaprevir has a long half-life, consistent with QD dosing.[9] Phase 1b studies demonstrated that faldaprevir QD combined with PegIFN/RBV was well tolerated and induced strong antiviral responses in treatment-naïve and -experienced HCV GT-1 patients.[10] Here, we report on the results of a phase 2b, multicenter, randomized, double-blind study of faldaprevir or placebo in combination with PegIFN/RBV in treatment-naïve, HCV GT-1-infected patients (SILEN-C1; **S**afety, and ant**I**vira**L** **E**ffect of faldaprevir i**N** hepatitis **C**).

Patients and Methods

Patients

Patients were enrolled at 89 centers in 15 countries (Argentina, Australia, Austria, Canada, Czech Republic, France, Germany, Republic of Korea, the Netherlands, Portugal, Romania, Spain, Switzerland, United Kingdom, and United States) between October 28, 2008, and April 6, 2009. Eligible patients were 18 to 65 years of age, had chronic hepatitis C infection of GT-1, and were therapy-naïve to IFN, PegIFN, and RBV or any other treatment for acute or chronic hepatitis C infection. In addition, patients had an HCV viral load (VL) of $\geq$100,000 IU/mL at screening, a liver biopsy within 24 months before study enrollment providing histologic evidence of any degree of chronic necroinflammatory activity or the presence of fibrosis, but no evidence of cirrhosis, and a normal retinal finding on fundoscopy within 6 months before enrollment. Patients with HCV of mixed GT, hepatitis B virus, human immunodeficiency virus (HIV), decompensated liver disease, or hyperbilirubinemia ($>$1.5 $\times$ upper limit of normal [ULN]) were excluded; patients with Gilbert's polymorphism were accepted. All patients provided written informed consent before 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, placebo-controlled trial (NCT00774397). Eligible treatment-naïve patients were randomized by a interactive voice response system (IVRS) to one of four treatment groups at a ratio of 1:1:2:2 (Fig. 1): placebo QD combined with PegIFN-α2a and RBV for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV; 120 mg faldaprevir QD combined with PegIFN-α2a and RBV for 24 weeks, starting with a 3-day lead-in (LI) phase of placebo plus PegIFN/RBV, and followed by an additional 24 weeks of PegIFN/RBV; 240 mg faldaprevir QD combined with PegIFN-α2a 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; and 240 mg faldaprevir QD combined with PegIFN-α2a and RBV for 24 weeks, followed by an additional 24 weeks of PegIFN/RBV. Randomization was stratified by VL ($<$600,000 and $\geq$600,000 IU/mL) and race (black, Asian, and all others). Randomization was not stratified by GT-1 subtype because the subtyping method available at the time of study initiation was unreliable. The role of the IL28B polymorphism was discovered after the study was fully enrolled. Patients and investigators were blinded to treatment groups until 24 weeks after the end of treatment; however, response-guided shortening of therapy was examined in some of the groups (see below), which led to partial unblinding at week 24 because HCV RNA levels were blinded up to

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Additional Supporting Information may be found in the online version of this article.

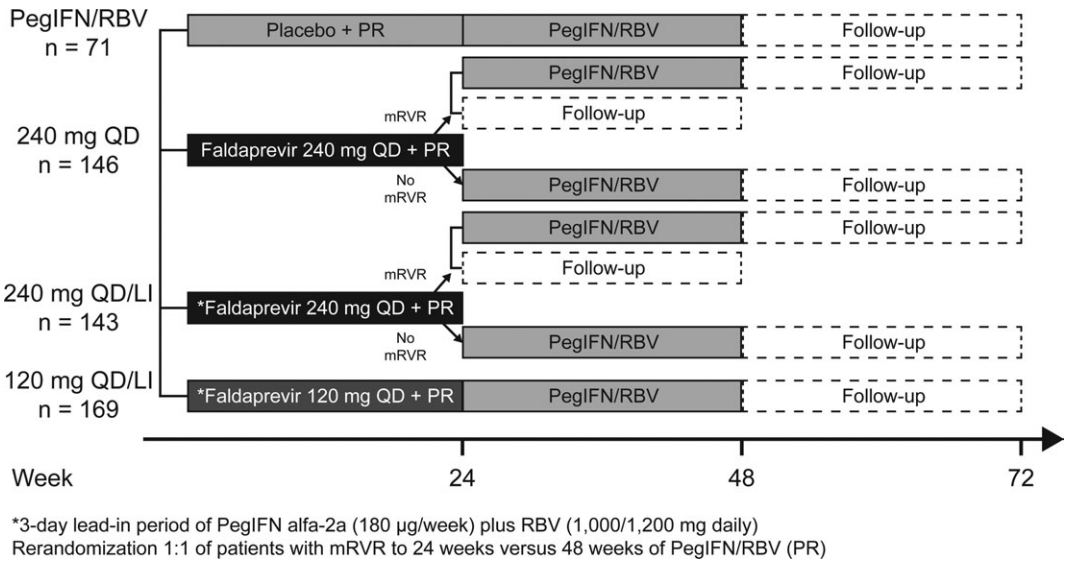


Fig. 1. Study design.

week 24 only. A loading dose of 480 or 240 mg faldaprevir was administered on the first day of faldaprevir treatment (on day 1 in the treatment groups without the 3-day PegIFN/RBV LI and on day 4 in the treatment groups with the 3-day PegIFN/RBV LI) in the 240 and 120 mg treatment groups, respectively. The rationale for the loading dose of faldaprevir (two times the daily dose in each arm) was to achieve steady-state concentrations more rapidly. A 3-day PegIFN/RBV LI strategy was also examined in two of the active arms. The rationale for the 3-day LI phase was that a short delay of the first intake of faldaprevir would allow sufficient levels of PegIFN and RBV to be achieved before the administration of faldaprevir and thus prevent the possibility of functional faldaprevir monotherapy. In both 240 mg treatment groups, all patients who achieved maintained rapid virologic response (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 (IVRS) 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-α2a was administered subcutaneously at a dose of 180 μg per week, and RBV was given orally at a dose of 1,000 (body weight: $<$75 kg) or 1,200 mg/day (body weight: $\geq$75 kg) in two divided doses. Faldaprevir and RBV were dosed with food. Patients continued to receive treatment with faldaprevir (or placebo) and PegIFN/RBV according to their treatment regimen, unless early withdrawal from medication occurred because of: HCV VL rebound by >1 $\log_{10}$ from nadir, or $\geq$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 (EVR), 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. Concomitant treatments with medications that are substrates of P-glycoprotein, uridine diphosphate glucuronosyltransferase (UGT)1A1, and cytochrome P450 3A4 or 2C9, with a narrow therapeutic range, were excluded.

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. Rebound was defined as HCV RNA >1 $\log_{10}$ from nadir, or $\geq$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 assay (Roche, Pleasanton, CA), at a central laboratory, at the time of screening

and during the treatment period at days 1 and 4 and weeks 1, 2, 4, 8, 10, 12, 16, 20, 24, 28, 36, and 48. The LLOQ was 25 IU/mL, and the LLOD was 17 IU/mL. At follow-up, plasma HCV RNA levels were measured 12 and 24 weeks after the end of all treatment. HCV GT for screening was determined using the TruGene HCV assay (Bayer, Leverkusen, Germany); because of the technical limitations of this genotyping assay,[11] 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 and for patients who discontinued study treatment with 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 (QIAGEN, Hilden, Germany). cDNA was synthesized using SuperScript III one-step reverse-transcription polymerase chain reaction (PCR) system platinum Taq DNA polymerase using GT-specific primers (Invitrogen, Carlsbad, CA). The length of amplified product generally limited 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 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA) detection system. The base calling with ABI's software allows for the detection of variants present at $\geq$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. Upon study initiation, the intensity of all 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). During the study, a rash management plan was introduced, which defined rash intensity as follows: mild (localized); moderate (diffuse, 30% to $\leq$70% body surface area); or severe (diffuse generalized, >70% body surface area or mucus membranes involved or organ dysfunction or signs of anaphylaxis or life threatening). Vital signs, electrocardiogram, and routine laboratory parameters were also evaluated.

Statistical Assessments

Descriptive statistics for efficacy and safety endpoints were calculated, along with two-sided *P* values for Fisher's exact test for equality to placebo, and 95% confidence intervals (CIs). The number of patients randomized to each group was based on an optimization approach that balances the cost (in terms of treated patients) of this phase 2 trial against the cost (in terms of hypothetical patients) of a failed phase 3 trial resulting from selection of the wrong dose. This approach indicated that 70 patients per regimen was optimal (Supporting Appendix). Because the faldaprevir 240 mg arms included rerandomization at week 24, the optimal number of patients in these arms was 140. All efficacy results relate to the per-protocol set of GT-1 patients (n = 423), whereas all safety results relate to all treated patients (n = 429).

A logistic regression analysis of baseline predictors of SVR was also performed for patients who received faldaprevir 240 mg without LI. Variables considered for inclusion in the model were subtype, IL28B GT (rs12979860) (CC, non-CC, or missing), alanine aminotransferase (ALT; normal or elevated), gamma-glutamyl transferase (GGT; normal or elevated), baseline HCV VL ($\geq$ or <800,000 IU/mL), gender, body mass index (BMI; < or $\geq$30), and time since diagnosis (<1 year, 1 to <5 years, or $\geq$5 years). Patients who provided consent were genotyped for IL28B GT (rs12979860) using allelic discrimination by TaqMan PCR. Individual regressions of each predictor were done as a screening with the intent that those with *P* values <0.2 would be selected for further study in a multiple logistic regression.

Results

Patient Disposition and Baseline Characteristics. Of 581 patients screened, 429 were randomized to treatment, whereas 152 did not meet entry criteria (Fig. 2). Of the 429 treated patients, 74 prematurely discontinued the trial medication (faldaprevir or placebo). Reasons for treatment discontinuation included AEs (n = 28), lack of efficacy (n = 23), refusal to continue the trial medication (n = 8), noncompliance with the protocol (n = 5), loss to follow-up (n = 3), and other reasons (n = 7).

Patients were evenly distributed over all dose groups with respect to gender, race, HCV RNA, GT, age, BMI, and IL28B GT (Table 1). Patients were

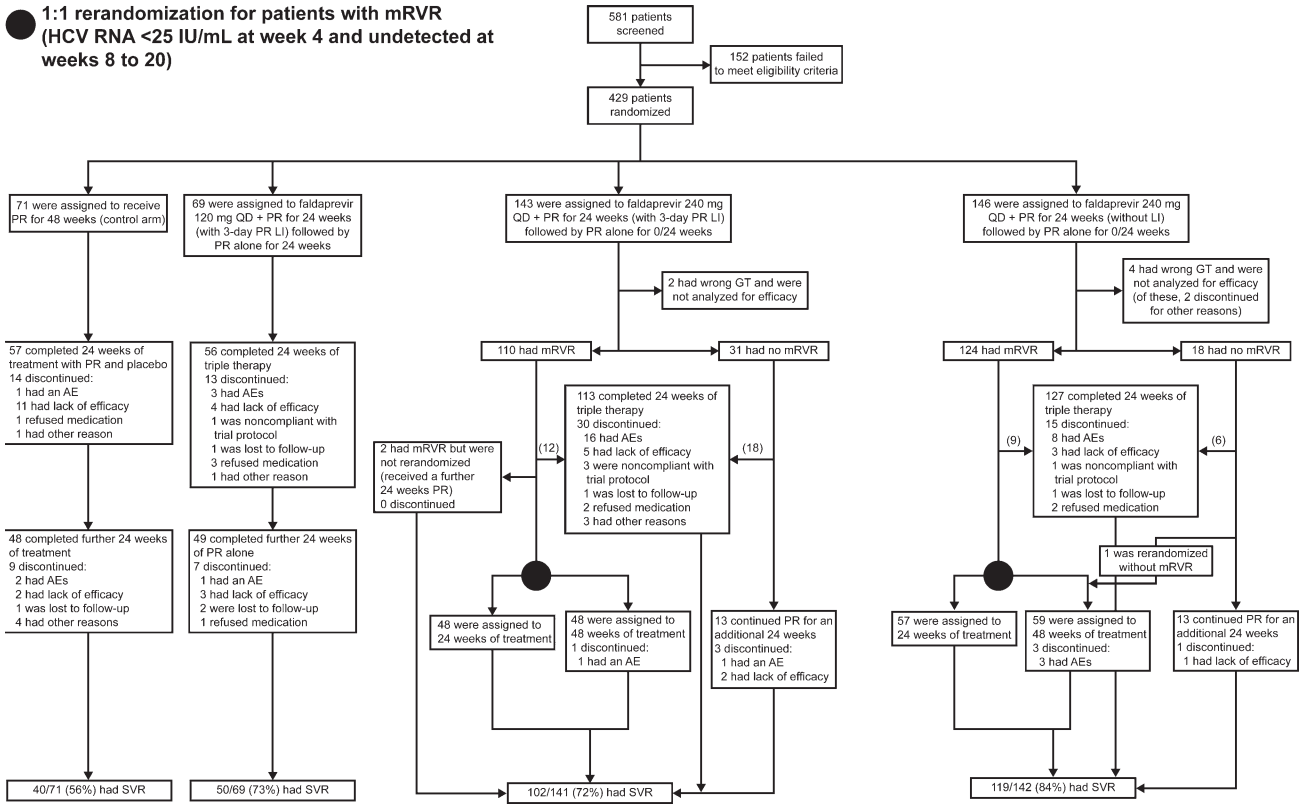


Fig. 2. Patient flow diagram.

Table 1. Summary of Baseline Characteristics

	PegIFN/RBV (n = 71)	Faldaprevir 120 mg QD/LI (n = 69)	Faldaprevir 240 mg QD/LI (n = 143)	Faldaprevir 240 mg QD (n = 146)	Total (n = 429)
Gender, n (%)					
Male	41 (58)	40 (58)	74 (52)	79 (54)	234 (55)
Female	30 (42)	29 (42)	69 (48)	67 (46)	195 (45)
Ethnicity, n (%)					
Asian	8 (11)	9 (13)	21 (15)	17 (12)	55 (13)
Black	4 (6)	1 (1)	1 (1)	4 (3)	10 (2)
White	57 (80)	58 (84)	119 (83)	122 (84)	356 (83)
Other	2 (3)	1 (1)	2 (1)	3 (2)	8 (2)
Age, years					
Mean	46	46	45	46	46
Standard deviation	10.9	10.9	10.2	10.5	10.5
BMI, kg/m^2					
Mean	26	26	26	26	26
Standard deviation	5.7	4.0	4.5	4.5	4.6
HCV RNA, log_{10} IU/mL					
Mean	6.41	6.19	6.45	6.41	6.39
Standard deviation	0.55	0.62	0.64	0.60	0.61
GT, n (%)					
1	1 (1)	0	0	0	1 (<1)
1a	32 (45)	19 (28)	67 (47)	51 (35)	169 (39)
1b	38 (54)	50 (72)	74 (52)	91 (62)	253 (59)
3a, 4a, 6e, 6l, 6q	0	0	2 (1)	4 (3)	6 (1)
IL28B GT					
(rs12979860), n (%) CC	11 (15)	8 (12)	19 (13)	22 (15)	60 (14)
Non-CC	29 (41)	33 (48)	53 (37)	48 (33)	163 (38)
Missing	31 (44)	28 (41)	71 (50)	76 (52)	206 (48)

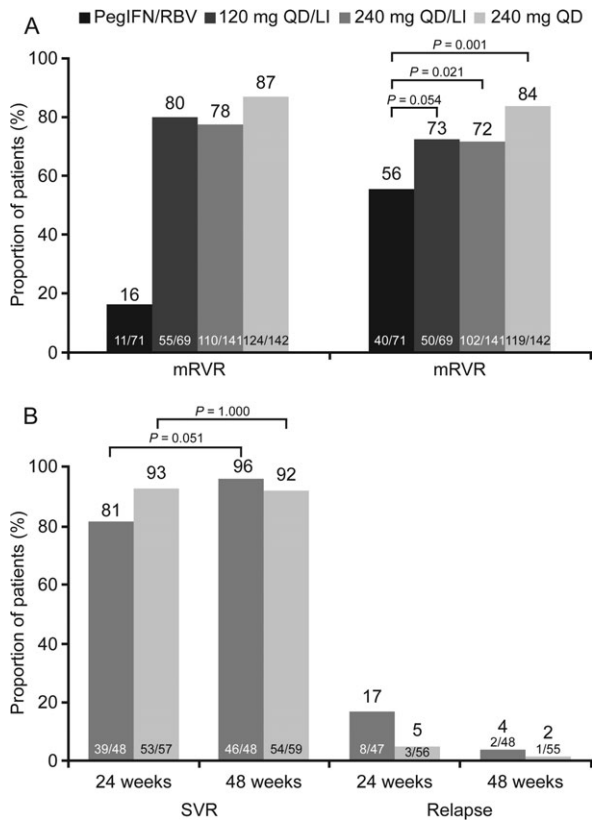


Fig. 3. Frequency of patients with (A) VR during and after treatment in all dose groups and (B) VR and relapse after treatment in patients who achieved mRVR and were rerandomized to 24 or 48 weeks of total treatment duration.

predominantly male (55%), mean age was 46 ± 11 years, mean BMI was 26.0 ± 4.6, and mean HCV RNA was 6.39 ± 0.61 $\log_{10}$ IU/mL. Analysis of IL28B GT (rs12979860) was performed retrospectively in 223 patients (the remaining patients did not provide consent for testing); of those tested, 27% were CC and 73% were non-CC. Six patients enrolled into the study and received study drug based on initial testing, but were found not to be infected with GT-1 by sequencing (GT-3, n = 2; GT-4, n = 1; GT-6, n = 3); all non-GT-1 patients achieved SVR. These patients are included in the safety analysis, but were excluded from the efficacy analysis.

Efficacy. SVR was achieved by 56% of patients in the placebo arm, compared to 72% of patients in the 120 mg QD/LI arm ($P = 0.054$), 72% of patients in the 240 mg QD/LI arm ($P = 0.021$), and 84% of patients in the 240 mg QD arm ($P = 0.001$; Fig. 3). The majority of patients treated with faldaprevir achieved mRVR with rates of 15%, 80%, 78%, and 87% in the placebo, 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD dose groups, respectively (Fig. 3). Virologic response (VR) is summarized in Table 2. In the placebo group, 11 of 71 patients (15%) relapsed. Thirty-one of 352 patients (9%) treated with faldaprevir relapsed: five of 69 (7%) in the 120 mg QD/LI group, 15 of 141 (11%) in the 240 mg QD/LI group, and 11 of 142 (8%) in the 240 mg QD group.

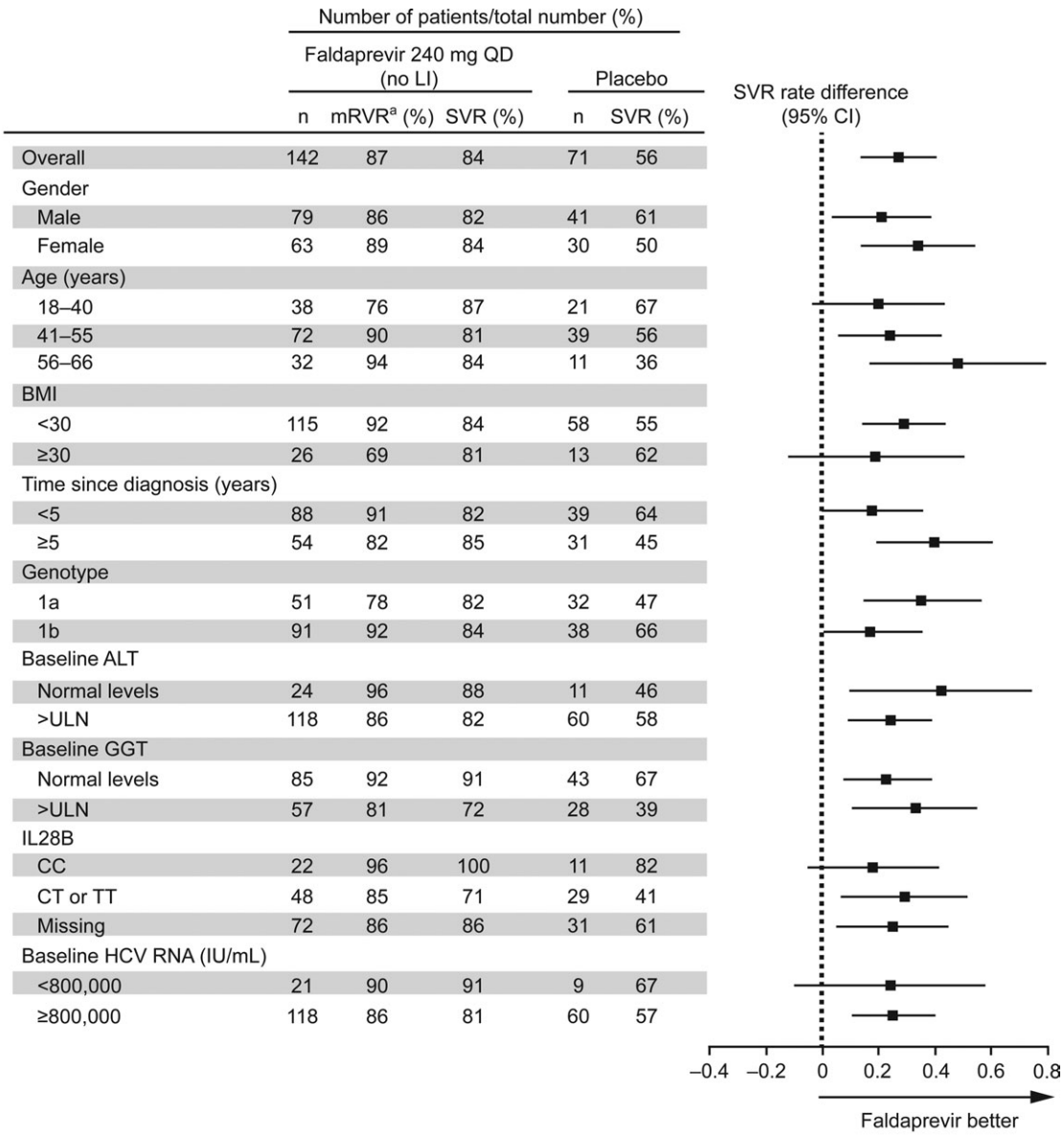
In the 240 mg QD/LI and 240 mg QD dose groups, 78% and 87% of patients, respectively, achieved mRVR and were eligible for rerandomization to either 24 or 48 weeks of PegIFN/RBV (Fig. 3). High rates of SVR (81% to 96%) were observed in patients with mRVR. In the 240 mg QD/LI arm, lower SVR (81% versus 96%; $P = 0.051$) and higher relapse (17% versus 4%) rates were observed in patients who achieved mRVR and were treated for 24 weeks, compared with those treated for 48 weeks. In contrast, 107 of 116 patients (92%) in the 240 mg QD dose group achieved SVR, irrespective of the duration of treatment (24 versus 48 weeks; $P = 1.000$); rates of relapse were also similar (5% versus 2%).

In patients who received the 240 mg QD dose without LI, SVR rates were consistently high across a wide range of patient subgroups (Fig. 4). Notably, the SVR rate for GT-1a patients was 82% (compared with 47% on PegIFN/RBV; $P = 0.0013$). All 22 patients (100%) with IL28B GT CC achieved SVR, compared with 82% with PegIFN/RBV alone. In this arm, the percentage of patients achieving mRVR and thus eligible for 24 weeks overall treatment duration was 87%, with similar rates across all subgroups, including non-CC patients. A univariate logistic regression analysis of baseline predictors of SVR in patients in the 240 mg QD dose group, considering IL28B GT, ALT, GGT, HCV VL, gender, BMI, and time since diagnosis, indicated that only GGT ($P = 0.013$, odds ratio [OR; 95% CI] = 3.32 [1.29, 8.59]) and IL28B

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

	Patients With VR, n (%)			
	PegIFN/RBV (n = 71)	Faldaprevir 120 mg QD/LI (n = 69)	Faldaprevir 240 mg QD/LI (n = 141)	Faldaprevir 240 mg QD (n = 142)<
SVR	40 (56)	50 (72)	102 (72)	119 (84)
Missing SVR	5 (7)	7 (10)	11 (8)	6 (4)
Nonresponders	10 (14)	1 (1)	5 (4)	1 (1)
Breakthrough during faldaprevir/placebo	2 (3)	4 (6)	7 (5)	5 (4)
Breakthrough during PegIFN/RBV	3 (4)	2 (3)	1 (1)	0
Relapse	11 (15)	5 (7)	15 (11)	11 (8)

Breakthrough was defined as HCV RNA rebound by >1 $\log_{10}$ from nadir or to ≥100 IU/mL if nadir was undetectable; nonresponders were defined as SVR not achieved, but no breakthrough or relapse; and relapse was defined as rebound after undetectable HCV RNA at end of treatment.



[a]mRVR: maintained rapid virologic response (HCV RNA <25 IU/mL at week 4 and undetected at weeks 8 to 20)

Fig. 4. Difference in rates of SVR between the treatment and control groups, according to subgroups.

($P = 0.154$) achieved the predefined significance level for multivariate testing. However, because 100% of patients with the IL28B CC GT achieved SVR, multiple variable regression was not performed. Within the 48 non-CC GT patients, the effect of GGT was slightly reduced (OR [95% CI] = 2.03 [0.56, 7.3]).

Rates of virologic breakthrough during faldaprevir treatment were comparable (3%-6%) with that observed in the placebo group (3%), but, in contrast to the placebo group, were predominantly associated with the selection of NS3 R155K or D168V variants for GT-1a or GT-1b patients, respectively. Three patients (1%) in the active arms experienced virologic rebound during PegIFN/RBV therapy after stopping faldaprevir therapy, including one R155K change (GT-1a), one without detectable resistant mutant (GT-1a), and one (GT-1a) with mixed substitutions at R155 and D168. Post-treatment rebound in the active arms from the nonresponder group was characterized by two R155K substitutions (one GT-1a in each 240 mg dose group) and the lack of detectable resistant mutants in the other five patients. Relapses among the faldaprevir treatment groups were observed in 31 of 352 patients (9%) with an undetectable VL at the end of treatment; viral sequencing of this patient group was characterized by predominant selection of R155K

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

	Patients With AEs, by Actual Treatment, n (%)			
	PegIFN/RBV (n = 71)	Faldaprevir 120 mg QD/LI (n = 69)	Faldaprevir 240 mg QD/LI (n = 140)	Faldaprevir 240 mg QD (n = 149)
Patients with any AE	67 (94)	67 (97)	138 (99)	147 (99)
Patients with serious AEs*	2 (3)	3 (4)	18 (13)	12 (8)
Discontinuations of faldaprevir/ placebo for AEs (total)	1 (1)	3 (4)	16 (11)	8 (5)
Rash	0	0	5 (4)	5 (3)
Photosensitivity	0	0	0	1 (<1)
Jaundice†	0	0	0	1 (<1)
Others‡	1 (1)	3 (4)	11 (8)	1 (<1)
Most frequent AEs				
Influenza-like illness	34 (48)	26 (38)	49 (35)	55 (37)
Nausea	14 (20)	18 (26)	66 (47)	66 (44)
Headache	27 (38)	29 (42)	46 (33)	51 (34)
Pruritus	12 (17)	22 (32)	48 (34)	56 (38)
Fatigue	24 (34)	19 (28)	33 (24)	39 (26)
Diarrhea	13 (18)	9 (13)	44 (31)	40 (27)
Rash	12 (17)	14 (20)	39 (28)	40 (27)
Asthenia	15 (21)	11 (16)	33 (24)	41 (28)
Jaundice	1 (1)	4 (6)	26 (19)	36 (24)
Insomnia	17 (24)	13 (19)	23 (16)	28 (19)
Alopecia	8 (11)	17 (25)	29 (21)	23 (15)
Decreased appetite	11 (15)	16 (23)	28 (20)	31 (21)
Myalgia	12 (17)	14 (20)	26 (19)	35 (23)
Dry skin	10 (14)	17 (25)	25 (18)	22 (15)
Vomiting	4 (6)	14 (20)	25 (18)	34 (23)
Pyrexia	11 (15)	10 (14)	28 (20)	31 (21)
Anemia	12 (17)	14 (20)	16 (11)	22 (15)

*Serious AEs experienced by patients were as follows (patients could experience more than one serious AE): PegIFN/RBV: cyst, photophobia, headache, migraine, and benign neoplasm; 120 mg QD/LI: prinzmetal angina, lymphopenia, and syncope; 240 mg QD/LI: anal abscess, lower respiratory tract infection, lymphangitis, subcutaneous abscess, upper respiratory tract infection, parapsoriasis, angina pectoris, microvascular angina, myocardial infarction, pyrexia (two patients), fatigue, headache, ischemic stroke, acute psychosis, suicide attempt, gall bladder polyp, road traffic accident, dehydration, calculus uretic, endometrial hyperplasia, and appendicectomy; 240 mg QD: pneumonia, upper respiratory tract infection, drug eruption (two patients), dermatitis atopic, eczema, palmar–plantar, photosensitivity reaction, pyrexia, febrile neutropenia, thrombocytopenia, cataract, depression, rectal hemorrhage, and diabetes mellitus.

†One patient discontinued faldaprevir (continued PegIFN/RBV) because of jaundice (patient choice related to cosmetic appearance) and experienced a bilirubin elevation of 12 × ULN with a ratio direct/total bilirubin of 0.07.

‡Patient discontinuations for "other" AEs were as follows: PegIFN/RBV: one patient with depression, aggression, and diarrhea; 120 mg QD/LI: one patient with lymphopenia and pyrexia, one with depression, and one with transaminase increase; 240 mg QD/LI: one patient with nausea and decreased appetite, one with acute psychosis, one with depression, one with a suicide attempt, one with myocardial infarction, fatigue, and deafness, one with microvascular angina, one with cough, two with nausea, one with vomiting, one with eczema, and one with parapsoriasis; 240 mg QD: one patient with thrombocytopenia and thrombocytopenic purpura.

variants in GT-1a patients (eight of 12) and D168V variants in GT-1b patients (11 of 19). Notably, five of six patients in the faldaprevir treatment groups with resistance substitutions detectable before treatment (two R155K in GT-1a and four D168 in GT-1b) achieved SVR.

Safety. Most AEs observed during or up to 30 days after the end of treatment with faldaprevir were those commonly related to PegIFN/RBV therapy (Table 3). Serious AEs were reported in two patients (3%) in the placebo group and 33 (9%) treated with faldaprevir (all serious AEs are described in the footnote of Table 3). Discontinuation of treatment resulting from an AE was lower for patients treated with placebo versus faldaprevir: one of 71 (1%) discontinued treatment in the control group, compared to three of 69 (4%), 16 of 140 (11%), and eight of 149 (5%) patients treated with 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD faldaprevir (Table 3). Of the 28 patients who discontinued faldaprevir or placebo because of AEs, 25 also discontinued PegIFN/RBV.

The primary AEs attributed to faldaprevir were mild gastrointestinal disorders (nausea, diarrhea, and vomiting), jaundice, pruritus, and rash. All AEs resolved during or after end of treatment. Rash and photosensitivity were higher in the 240 mg groups, compared to placebo and the 120 mg group. Probability of occurrence of rash or photosensitivity reactions tended to increase with increasing median trough plasma levels of faldaprevir. Rashes had an erythematous, macular, or papular morphology, preferentially affecting the trunk, arms, and legs, and usually

Table 4. Maximum or Minimum On-Treatment Values in Safety Laboratory Parameters During 24 Weeks of Treatment With PegIFN/RBV ± Faldaprevir, by Treatment Given

n (%)	PegIFN/RBV (n = 70)	Faldaprevir 120 mg QD/LI (n = 69)	Faldaprevir 240 mg QD/LI (n = 140)	Faldaprevir 240 mg QD (n = 148)
Bilirubin (0.1 to 1.0 mg/dL)				
≤1.0 × ULN	58 (83)	18 (26)	14 (10)	4 (3)
>1.0 to 1.5 × ULN	10 (14)	18 (26)	12 (9)	13 (9)
>1.5 to 2.5 × ULN	2 (3)	17 (25)	34 (24)	58 (39)
>2.5 to 5.0 × ULN	0	16 (23)	62 (44)	66 (45)
>5 × ULN	0	0	18* (13)	7* (5)
ALT (0 to 56 U/L)				
≤1.25 × ULN	20 (29)	13 (19)	30 (21)	48 (32)
>1.25 to 2.5 × ULN	36 (51)	36 (52)	70 (50)	72 (49)
>2.5 to 5.0 × ULN	12 (17)	18 (26)	37 (26)	25 (17)
>5 to 10 × ULN	2 (3)	2 (3)	1 (1)	3 (2)
>10 × ULN	0	0	2 (1)	0
Hemoglobin (12.5-18.0 g/dL)				
≥10 g/dL	55 (79)	59 (86)	121 (86)	118 (80)
8.5 to <10 g/dL	11 (16)	8 (12)	15 (11)	23 (16)
7.5 to <8.5 g/dL	3 (4)	2 (3)	3 (2)	4 (3)
6.5 to <7.5 g/dL	1 (1)	0	1 (1)	3 (2)
<6.5 g/dL	0	0	0	0
Absolute neutrophil count (1,960-7,230/μL)				
≥1,300/μL	23 (33)	20 (29)	52 (37)	57 (39)
1,000 to <1,300/μL	15 (21)	18 (26)	47 (34)	38 (26)
750 to <1,000/μL	22 (31)	19 (28)	28 (20)	27 (18)
500 to <750/μL	6 (9)	11 (16)	9 (6)	21 (14)
<500/μL	4 (6)	1 (1)	4 (3)	5 (3)

*The 25 patients who experienced bilirubin elevations >5 × ULN are further characterized in Supporting Table 1.

occurred during the first 12 weeks of treatment. Mucus membranes and other organs were not affected in any patient. There were no cases of Stevens-Johnson syndrome (SJS), erythema multiforme, or drug rash with eosinophilia and systemic symptoms (DRESS). The majority of cases were mild and were managed without treatment interruption, in most cases, by applying topical treatments and, rarely, systemic corticosteroids (<5%). Photosensitivity mostly manifested as mild erythema limited to sun-exposed areas of the body and led to one discontinuation. Severe rash events were observed in 11 patients (3% in the faldaprevir groups): five patients (4%) in the 240 mg QD/LI group and six (4%) in the 240 mg QD group. Ten patients in the 240 mg dose groups (3%) discontinued faldaprevir because of rash, which was classified as severe in eight of these cases.

At the higher doses of 240 mg QD, 20% to 25% of patients experienced jaundice (usually mild) as a result of dose-dependent, isolated, unconjugated hyperbilirubinemia associated with faldaprevir; rates of mild jaundice were similar for placebo and 120 mg QD (Table 3). Hyperbilirubinemia was rapidly reversible (bilirubin normalized in all patients subsequent to cessation of faldaprevir dosing) and not associated with liver injury, hemolysis, or any other clinical symptoms. Changes in safety laboratory values were consistent with those observed with PegIFN/RBV (Table 4). Importantly, there was no additional effect of faldaprevir on hemoglobin levels or white blood cells, compared to the control group; the rate of erythropoietin was similar in the placebo and active arms (5% to 12%).

Discussion

The PI faldaprevir, dosed QD in combination with PegIFN and RBV, increased SVR rates of treatment-naïve GT-1 patients from 56% in the placebo group to as high as 84% with 240 mg faldaprevir. SVR rates were similar with this dose in patients with historically less-favorable IL82B GT and HCV GT-1a. Interestingly, patients in the 120 mg QD/LI group had similar EVR and SVR rates to those in the 240 mg QD/LI group, suggesting a lack of a dose effect on VR at the higher dose. Furthermore, although not directly compared, SVR rates observed with all dose regimens of faldaprevir and PegIFN/RBV appear at least similar to those reported with the recently approved PIs boceprevir and telaprevir (68% and 73%, respectively).[3,5]

Response-guided therapy (RGT) was assessed in both 240 mg dose groups, where 78% and 87% of patients with or without LI achieved mRVR, respectively, defined as HCV RNA <LLOQ at week 4 and

<LLOD at weeks 8 to 20. Thus, the majority of patients met the response criteria for rerandomization to either stopping all treatment after 24 weeks or continuation of PegIFN/RBV to week 48. All patients who were not eligible for rerandomization continued PegIFN/RBV to week 48. Importantly, patients achieving mRVR who stopped all treatment at week 24 in the 240 mg QD dose group showed equivalent SVR rates as those who continued PegIFN/RBV to week 48. Because these data were derived in a randomized fashion, they support the application of RGT with 24 weeks of overall treatment duration for treatment-naïve GT-1 patients achieving mRVR.

Clinical trials of boceprevir and telaprevir also included the option for shortened treatment duration, but incorporated more-stringent criteria (which included HCV RNA <LLOD at week 4) than this study.[3,5] When the criteria used in the telaprevir studies to identify patients eligible for shortened treatment duration (HCV RNA <LLOD at weeks 4 and 12) were applied to this data set, up to 75% met the criteria, suggesting that the majority of patients treated with faldaprevir plus PegIFN/RBV may be eligible for 24 weeks of therapy. Furthermore, these data support the application of less-stringent criteria at treatment week 4 (<25 IU/mL detected or undetected), which may be acceptable for the determination of patients who can be treated for shorter duration with faldaprevir plus PegIFN/RBV.

HCV NS3/4A PIs have been shown to rapidly select for the emergence of resistance mutations when administered as monotherapy.[10,12] Therefore, the effect of 3 days of pretreatment of patients with PegIFN and RBV before adding faldaprevir was assessed directly by comparing 240 mg QD dose groups with or without LI. The rationale was that the short delay of the first intake of faldaprevir would prevent the possibility of functional PI monotherapy. Surprisingly, the administration of a 3-day LI with PegIFN/RBV before initiation of faldaprevir resulted in approximately 10% lower rates of mRVR and SVR, compared with faldaprevir initiated simultaneously with PegIFN/RBV. A similar negative effect was observed in a second independent phase 2 trial of faldaprevir in patients who had nonresponse to previous PegIFN/RBV treatment.[13] Although the reasons for poor response with short LI are unknown, rapid and profound inhibition of HCV replication might restore IFN responsiveness, as suggested by the decrease of plasma levels of IFN-inducible protein 10, a lymphocyte chemokine indicative of endogeneous activation of host IFN pathways, in HCV patients treated with IFN-free regimens.[14] However, further research is required to test this hypothesis. Although the reasons for lower response rates with 3-day LI are not fully understood, this strategy was not selected for further investigation.

Breakthroughs and relapses in the faldaprevir treatment groups were rare and usually associated with the selection of common NS3 PI-resistant variants, whereas patients failing PegIFN/RBV had wild-type NS3 sequences detected, with the exception of one patient who had selected for a D168E mutant, a previously observed natural polymorphism that also shifts potency of some PIs. Faldaprevir selected NS3 mutants predominantly encoded for R155K and D168V in GT-1a and GT-1b, respectively. Patients who experienced postfaldaprevir treatment rebound (either relapser and rebound from nonresponse) selected for similar NS3 amino acid changes, although 29% of isolates across the faldaprevir treatment groups encoded for virus that lacked known resistance mutants. *In vitro* studies have demonstrated 100-fold to 500-fold reduced sensitivity of various viral GT-1a strains carrying the R155K substitution, whereas D168V substitutions in GT-1b strains conferred >1,000-fold reduced sensitivity to faldaprevir.[15] The clinical data indicate that these shifts in sensitivity cannot be offset by the increase in faldaprevir exposure achieved by dose doubling from 120 to 240 mg QD.

The most frequent AEs were those typical for PegIFN/RBV therapy. Although 120 mg QD faldaprevir had a safety profile similar to PegIFN/RBV (only pruritus and vomiting increased), higher frequencies were reported for skin rash, photosensitivity, jaundice, nausea, and diarrhea with the 240 mg QD dose. However, the vast majority of events were mild or moderate in intensity and only 4% to 11% of patients discontinued faldaprevir at 120 or 240 mg QD. Jaundice was, in all but one case, the result of isolated increases of unconjugated bilirubin (one patient with normal plasma bilirubin), was rapidly reversible after cessation of faldaprevir, and was not associated with signs of liver toxicity or excess hemolysis; patients had no other symptoms, and only one patient in the trial discontinued because of jaundice. *In vitro* studies demonstrated that faldaprevir mediated inhibition of the bilirubin-conjugating enzyme UGT1A1 and, to a lesser extent, the organic anion-transporting polypeptide 1 and multidrug-resistant protein 2 transporters, which appear to be the key drivers of this finding.[16] This effect is comparable with that of other PIs in development for HCV[17] or in clinical use for HIV (e.g., atazanavir) treatment, which is not considered a sign of hepato- or hematotoxicity.[18] Skin rash and photosensitivity

reactions, which were more frequent with the 240 mg QD dose, were usually mild and could be managed without treatment modifications, in most instances. There were few discontinuations resulting from skin events and no cases of DRESS syndrome, SJS, or erythema multiforme. Of note, there was no effect of faldaprevir on hemoglobin levels, red blood cell counts, or leukocyte counts, suggesting that anemia and leukocytopenia reported for some other PIs are not a class effect, but rather compound-specific side effects.

A potential limitation of this trial was the exclusion of patients with liver cirrhosis; this was because of the lack of phase 1 safety data in this patient population at the initiation of this study. However, tolerability, safety, and efficacy of 240 mg QD faldaprevir with PegIFN/RBV given for four weeks in patients with compensated liver cirrhosis (Child-Pugh score) was demonstrated to be similar to patients without cirrhosis in recently completed phase 1 and 2 trials.[19,20] Importantly, the PK characteristics were unchanged in patients with cirrhosis. In addition, degree of liver fibrosis was not collected prospectively in this study, precluding any analysis of the association of fibrosis stage on the efficacy and safety of faldaprevir. Lastly, because of the inclusion of RGT in some, but not all, treatment arms, the study was only fully blinded up to treatment week 24.

In this large, phase 2 study of faldaprevir QD, in combination with PegIFN/RBV, cure of infection (SVR) was achieved in up to 84% of HCV GT-1 patients, with more than 80% meeting VR criteria for shortened treatment duration (24 weeks). Overall, the treatment regimen was safe and tolerable. Confirmatory phase 3 trials testing 120 and 240 mg QD faldaprevir without LI, in combination with PegIFN/RBV, are ongoing in treatment-naïve and -experienced patients, as well as patients with HCV/HIV coinfection.

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