

Randomized Trial of Peginterferon alfa-2b and Ribavirin for 48 or 72 Weeks in Patients with Hepatitis C Virus Genotype 1 and Slow Virologic Response

Maria Buti,¹ Yoav Lurie,² Natalia G. Zakharova,³ Natalia P. Blokhina,⁴ Andrzej Horban,⁵ Gerlinde Teuber,⁶ Christoph Sarrazin,⁶ Ligita Balciuniene,⁷ Saya V. Feinman,⁸ Rab Faruqi,⁹ Lisa D. Pedicone,⁹ and Rafael Esteban¹; for the SUCCESS Study Investigators

The benefit of extending treatment duration with peginterferon (PEG-IFN) and ribavirin (RBV) from 48 weeks to 72 weeks for patients with chronic hepatitis C genotype 1 infection has not been well established. In this prospective, international, open-label, randomized, multicenter study, 1,428 treatment-naïve patients from 133 centers were treated with PEG-IFN alfa-2b (1.5 µg/kg/week) plus RBV (800-1,400 mg/day). Patients with detectable hepatitis C virus (HCV) RNA and a ≥ 2 -log₁₀ drop in HCV RNA levels at week 12 (slow responders) were randomized 1:1 to receive 48 weeks (n = 86) or 72 weeks (n = 73) of treatment. Sustained virologic response (SVR) rates were 43% in slow responders treated for 48 weeks and 48% in slow responders treated for 72 weeks ($P = 0.644$). Relapse rates were similar in slow responders treated for 48 or 72 weeks (47% versus 33%, $P = 0.169$). The safety profile was similar in both treatment arms; serious adverse events leading to discontinuation of treatment were observed in 3.5% of slow responders treated for 48 weeks and 8.2% of those treated for 72 weeks. Among slow responders with a < 2 -log drop in HCV RNA at week 8, SVR was 39% in the 72-week arm and 19% in the 48-week arm. **Conclusion:** These data suggest that 48 weeks of therapy with PEG-IFN alfa-2b plus RBV (800-1,400 mg/day) should remain a standard-of-care treatment for treatment-naïve G1 slow responders. (HEPATOLOGY 2010;52:1201-1207)

Peginterferon (PEG-IFN) alfa-2a or alfa-2b plus ribavirin (RBV) for 48 weeks is the standard of care for patients with chronic hepatitis C (CHC) genotype 1 (G1) infection and achieves sustained virologic response (SVR) in 40%-52% of treated patients.¹⁻⁴ Because these response rates are largely unsatisfactory, an individualized approach to treatment of hepatitis C is increasingly being adopted. In this approach, total treatment duration is determined according to the first time during therapy that hepatitis C virus (HCV) RNA becomes undetectable.

The length of time that each patient maintains undetectable HCV RNA while on treatment is directly correlated to the likelihood of SVR.^{4,5}

Several studies adopting this approach have shown that extending therapy to 72 weeks may increase SVR rates in selected G1 patients.⁶⁻¹¹ However, the on-treatment virologic criteria used to select patients for extended therapy vary across studies. Accurately defining which G1 patients will benefit from extended treatment is important, because prolonged treatment is associated with increased adverse events and higher costs.

Abbreviations: cEVR, complete early virologic response; CHC, chronic hepatitis C; CI, confidence interval; G1, genotype 1; HCV, hepatitis C virus; PEG-IFN, peginterferon; RBV, ribavirin; SVR, sustained virologic response.

From the ¹Liver Unit, Valle d'Hebron (Ciberehd) University Hospital, and Biomedical Research Center Network in the Area of Hepatic and Digestive Disorders of the Carlos III Health Institute, Barcelona, Spain; the ²Sourasky Medical Center, Tel Aviv, Israel; the ³St. Petersburg Municipal Center of Prophylactic AIDS and Obvodny Channel, St. Petersburg, Russia; ⁴Clinical Infection Hospital #1, Volokolamskoye Shosse, Moscow, Russia; the ⁵Warsaw Medical University & Hospital of Infectious Diseases, Warsaw, Poland; ⁶J.W. Goethe University Hospital, Frankfurt, Germany; the ⁷Vilnius University Hospital of Tuberculosis and Infection Diseases, Santariskės, Lithuania; ⁸Mount Sinai Hospital, Toronto, Ontario, Canada; and ⁹Schering-Plough Corporation, Whitehouse Station, NJ.

Received April 30, 2010; accepted June 10, 2010.

Supported by Schering-Plough Corporation (currently Merck & Co., Inc.).

Address reprint requests to: Dr. Maria Buti, Paseo Valle de Hebron 119-129, Servicio de Hepatologi, Hospital Vall d'Hebrón and CIBERhd del Instituto Carlos III, Barcelona, Spain 08036. E-mail: mbuti@vhebron.net; fax: (34)-934274495.

The aim of this large, randomized, international, multicenter study—known as the SUCCESS study—was to determine whether an increase of treatment duration to 72 weeks instead of the standard 48 weeks was associated with an increase in SVR in patients with HCV G1 who showed a slow virologic response.

Patients and Methods

Patient Selection. Patients were eligible for enrollment if they were treatment-naïve, aged 18–70 years, and had compensated CHC (anti-HCV-positive with detectable HCV RNA). All patients had alanine aminotransferase levels above the upper limit of normal and a liver biopsy performed within 18 months prior to screening that confirmed a histologic diagnosis of chronic hepatitis. Key exclusion criteria were body weight >125 kg; coinfection with hepatitis B virus, human immunodeficiency virus, or both; or any cause of liver disease other than CHC.

Study Design. This was a prospective, open-label, randomized, multicenter, international study conducted in 133 centers between December 2004 and May 2008.

Patients received PEG-IFN alfa-2b 1.5 $\mu\text{g}/\text{kg}/\text{week}$ (PegIntron; Schering-Plough, Kenilworth, NJ) plus RBV 800–1,400 mg/day (Rebetol; Schering-Plough) according to body weight (800 mg for patients weighing <65 kg; 1,000 mg for patients weighing 65–85 kg; 1,200 mg for patients weighing 85–105 kg; and 1,400 mg for patients weighing >105 kg but <125 kg). All patients were treated for an initial 12-week period, and further treatment duration was set in accordance with week 12 HCV RNA levels. According to the current clinical guidelines and standard of care,¹² patients with a <2-log decline from baseline at week 12 were withdrawn from treatment, whereas those with undetectable HCV RNA (complete early virologic response [cEVR]) were treated for an additional 36 weeks (group C; total of 48 weeks of treatment).

Patients with detectable HCV RNA and a ≥ 2 -log drop at week 12 (partial early virologic response) continued to receive the same treatment regimen until week 24. At week 24, patients with detectable HCV RNA were withdrawn from treatment.¹² Those patients with undetectable HCV RNA at week 24

were considered slow responders and randomized 1:1 to treatment for an additional 24 weeks (group A; total of 48 weeks of therapy) or 48 weeks (group B; total of 72 weeks of therapy). Randomization was performed independent of sponsor and investigators through a data fax response system using a computer-generated randomization scheme in blocks of four (Everest Clinical Research Services, Markham, Ontario, Canada). Study groups were stratified by center. Standard criteria were employed for dose reduction and treatment discontinuation in patients experiencing hematologic toxicity. Compliance was monitored by comparing the amounts of dispensed and returned medication to determine whether treatment had been taken per protocol in the preceding period.

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All patients provided voluntary written informed consent prior to trial entry. The study sponsor and the academic principal investigators (MB and RE) were responsible for the study design, protocol, statistical analysis plan, and data analysis. The principal investigators had unrestricted access to the data and wrote the manuscript, and the sponsor performed the statistical analysis. All authors approved the final draft of the manuscript. This study is registered with clinicaltrials.gov as NCT00265395.

Patient Evaluation. HCV RNA analyses were performed at a central laboratory using quantitative reverse transcriptase polymerase chain reaction (COBAS Taqman, Roche) assay with a lower limit of quantitation of 30 IU/mL. HCV RNA levels were evaluated at screening, baseline, and treatment weeks 4, 8, 12, 24, 48, and 72 (group B) and at week 24 follow-up. Trugene HCV Genotyping (Bayer HealthCare LLC, Tarrytown, NY) was used to determine HCV genotype.

Study Endpoints. The study was powered to assess the superiority of 72 weeks compared with 48 weeks of treatment in slow responders. The intent-to-treat population included all patients who were randomized and received at least 1 dose of either PEG-IFN alfa-2b or RBV. The primary efficacy analysis was to compare the percentage of slow responders attaining SVR (undetectable HCV RNA 24 weeks after receiving the last dose of therapy) when treated for the longer

duration of 72 weeks with the standard treatment duration of 48 weeks in patients with slow virologic response (group A versus group B). Secondary endpoints were end-of-treatment virologic response (undetectable HCV RNA at the end of therapy), relapse rates (end-of-treatment response, but with detectable HCV RNA at the end of the 24-week follow-up period), and safety and tolerability. Positive and negative predictive values for a ≥ 2 -log decline in HCV RNA at week 8 were calculated. All patients who received at least 1 dose of either PEG-IFN alfa-2b or RBV were included in the safety analysis. The modified World Health Organization grading system was used to grade the severity of adverse events. Investigators were responsible for assigning the relatedness to treatment for each adverse event.

Sample Size. It was estimated that 120 slow responders would be required to detect a difference in SVR rates of 25% between groups A and B (i.e., 45% in group A and 70% in group B, with a 2-sided alpha of 0.05) with at least 80% power. Based on the expectation that approximately 10% of patients would meet the slow-responder criterion, total enrollment was estimated at 1200 patients.

Statistical Analysis. The primary efficacy analysis was an asymptotic z test with a null hypothesis of no difference in the rate of SVR in slow responders between groups A and B. In addition, the two-sided 95% confidence interval (CI) for the difference in SVR rates was used to estimate the degree of variability between the two groups. Similar methods were applied to secondary efficacy analyses. Continuous variables were summarized using descriptive statistics, and categorical variables were summarized using frequency counts and percentages. Whenever appropriate, P values and 95% CIs were calculated for the relevant statistics.

A predefined "per protocol" analysis included patients who received study medication, did not deviate significantly from the entry criteria, and did not take any prohibited medication. Additionally, an ad hoc analysis included all treated patients who met the criteria for fast or slow response and who completed the assigned duration of therapy.

Results

Patient Population. The study enrolled 1,428 treatment-naïve patients with CHC G1 infection at 133 study sites. Of the 1,428 patients enrolled, 1 did not receive the study drug; thus, 1,427 patients received treatment per protocol. In total, 159 patients (11.1%) met the slow responder criteria and were randomized

to 48 ($n = 86$) or 72 ($n = 73$) weeks of treatment. Of the remaining patients, 816 (57.2%) attained a cEVR and were treated for 48 weeks (group C) and 452 (31.7%) either withdrew from the study at week 12 or were nonresponders, and treatment was stopped as defined in the protocol (Fig. 1). Patient demographics were generally similar across the treatment groups (Table 1). A baseline viral load $>800,000$ IU/mL was more common in slow responders than patients with cEVR.

In total, eight patients in group A and 17 patients in group B failed to complete the study (Fig. 1). All eight patients in group A discontinued treatment between weeks 24 and 48. Of the 17 slow responders in group B who failed to complete treatment, 11 discontinued treatment between weeks 24 and 48, and six discontinued treatment between weeks 49 and 72. Reasons for discontinuation in group B were adverse events ($n = 6$ [4 prior to week 48 and 2 after week 48]), lost to follow-up ($n = 1$ [prior to week 48]), did not wish to continue ($n = 6$ [4 prior to week 48 and 2 after week 48]), noncompliance ($n = 2$ [1 prior to week 48 and 1 after week 48]), and other reasons ($n = 2$ [1 prior to week 48 and 1 after week 48]).

Virologic Response. In total, 721 of 1,427 (50.5%) patients who received treatment per protocol attained an SVR. Among patients with cEVR, 27.5% had undetectable HCV RNA at week 4 of treatment (rapid virologic response), and 71.4% had undetectable HCV RNA at week 8.

In the intent-to-treat analysis, SVR rates were similar in groups A and B (43% versus 48%; $P = 0.6445$) and higher in group C (80%; $P < 0.0001$ versus group A) (Fig. 2). End-of-treatment response was 83%, 70%, and 89% in groups A, B, and C, respectively. Relapse rates were 47% for group A and 33% for group B; however, the difference was not statistically significant ($P = 0.1699$). Relapse rates were significantly lower for group C compared with group A (10% versus 47%; $P < 0.0001$).

Among adherent patients (those who received $\geq 80\%$ of the planned dose of each drug for $\geq 80\%$ of the assigned treatment duration), SVR rates were 44% for group A and 57% for group B ($P = 0.20$); SVR rates in the per-protocol population were 44% and 49%, respectively ($P = 0.63$). Similarly, SVR rates in the completers population were 46% and 57% ($P = 0.28$), and relapse rates were 47.1% and 28.9% in the 48- and 72-week treatment arms, respectively.

Variables Associated with SVR. Slow responders <40 years old were significantly more likely to attain an SVR compared with those >60 years old (odds

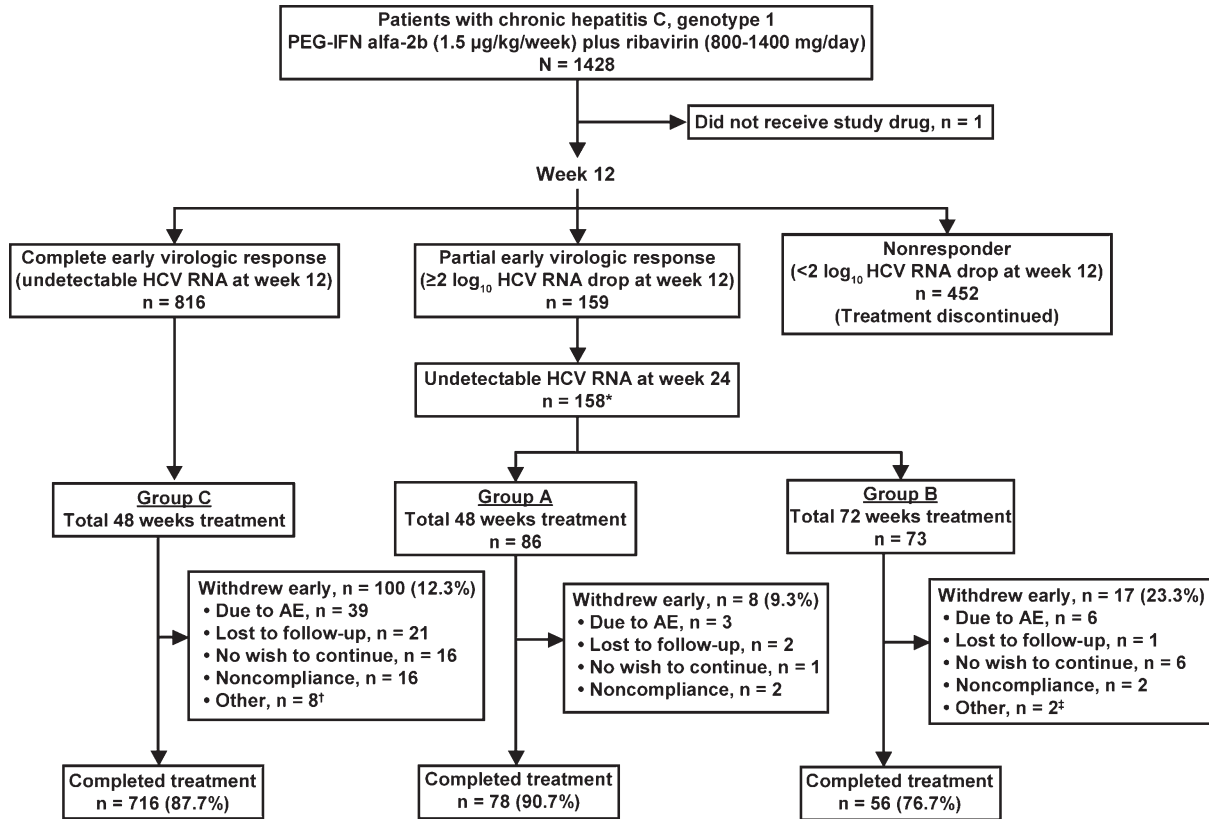


Fig. 1. Study design. *One patient with partial early virologic response and detectable HCV RNA at week 24 was randomized to group A. †One administrative, two deaths, and five ineligible. ‡One administrative and one treatment failure. AE, adverse event.

ratio 3.991; 95% CI 1.043-15.277; *P* = 0.017). Other variables including weight, treatment arm (group A versus group B), and week 12 HCV RNA levels (<50 versus >5,000 IU/mL or 50-5,000 versus >5,000 IU/mL) did not achieve any statistical significance. There was a trend toward a significant associa-

tion between week 8 viral load (<2-log versus ≥2-log drop from baseline), 72 weeks of treatment, and SVR among slow responders (odds ratio 2.504; 95% CI 0.948-6.613; *P* = 0.064). The negative predictive value for a <2-log decline at week 8 was 81% among patients treated for 48 weeks and 62% among those

Table 1. Patient Demographics and Disposition

Demographic	Group A (n = 86):	Group B (n = 73):	Group C (n = 816):	Nonresponders (n = 452*)
	Slow Responder, 48 Weeks of Treatment	Slow Responder, 72 Weeks of Treatment	cEVR, 48 Weeks of Treatment	
Age in years, mean (SD)	44.5 (9.9)	46.5 (11.6)	40.4 (11.4)	44.5 (11.9)
White, n (%)	86 (100)	70 (95.9)	783 (96.0)	429 (94.9)
Female, n (%)	34 (39.5)	27 (37.0)	309 (37.9)	175 (38.7)
Weight in kg, mean (SD)	78.0 (15.2)	77.5 (16.6)	76.5 (14.7)	74.7 (14.2)
Baseline HCV RNA in IU/mL, median log	6.54	6.64	6.42	6.65
Alanine aminotransferase level in U/L, mean (SD)	76 (48)	85 (71)	100 (70)	91 (65)
Baseline viral load, n (%)				
≤400,000	3 (3.5)	1 (1.4)	132 (16.2)	10 (2.2)
>400,000-800,000	8 (9.3)	4 (5.5)	90 (11)	33 (7.3)
>800,000	75 (87.2)	68 (93.2)	594 (72.8)	408 (90.3)
Change in HCV RNA between screening and baseline, n (%)				
Decreased by ≥1 log	3 (3.5)	0 (0)	34 (4.2)	7 (1.6)
Increased by ≥1 log	0 (0)	1 (1.4)	12 (1.5)	4 (0.9)

*Includes 371 nonresponders and 81 patients who withdrew from therapy prior to week 12.

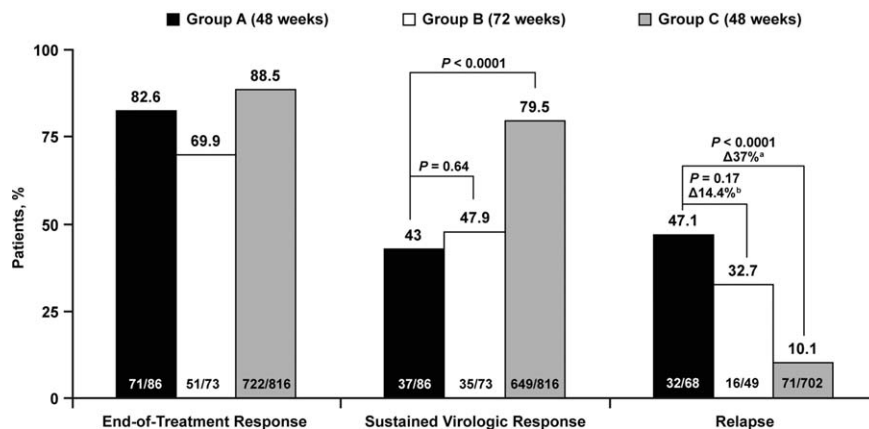


Fig. 2. Virologic response rates. ^a95% CI 24.9%-49%. ^b95% CI -3.3%-32.1%.

treated for 72 weeks (Fig. 3). Thus, absence of a ≥ 2 -log decline in HCV RNA at week 8 was a strong predictor for treatment failure with a 48-week treatment duration, but was less predictive if the treatment duration was 72 weeks. In addition, among the slow responders with a < 2 -log decline in HCV RNA at week 8, SVR was attained by 19% of patients treated for 48 weeks and 39% of those treated for 72 weeks. Among slow responders with a ≥ 2 -log decline in HCV RNA at week 8, treatment outcomes were similar regardless of treatment duration.

Safety and Tolerability. Safety and tolerability were generally similar across all treatment groups (Table 2). Serious adverse events were similar across the treatment arms; however, adverse events leading to early withdrawal from therapy appeared slightly higher in group B compared with group A.

Discussion

This was the largest prospective, randomized study of patients with hepatitis C G1 infection and a slow virologic response. These data show that a weight-based regimen of PEG-IFN alfa-2b plus RBV for 72 weeks resulted in a similar rate of SVR compared with the same regimen administered for 48 weeks. Although there was a numerical trend for improved SVR in the 72-week treatment arm, this failed to achieve statistical significance. This observation has important implications for clinical practice because of the increasing tendency, as recommended by some guidelines,¹² to extend treatment duration beyond 48 weeks for slow virologic responders and, occasionally, for G1-infected patients with detectable HCV RNA at week 4. This practice results in an increase in adverse events and cost of therapy without a clear benefit in increasing SVR.

The results of two studies suggest that treatment with PEG-IFN alfa 2a plus RBV for 72 weeks

increases SVR rates in patients with varying definitions of slow response compared with the standard 48-week treatment. However, in these studies (one prospective study in patients with detectable HCV RNA at week 4, and one retrospective analysis of patients with HCV RNA ≥ 50 IU/mL at week 12 and < 50 IU/mL at week 24),^{6,7} patients were treated with a fixed dose of RBV (800 mg), resulting in SVR rates of 17% and

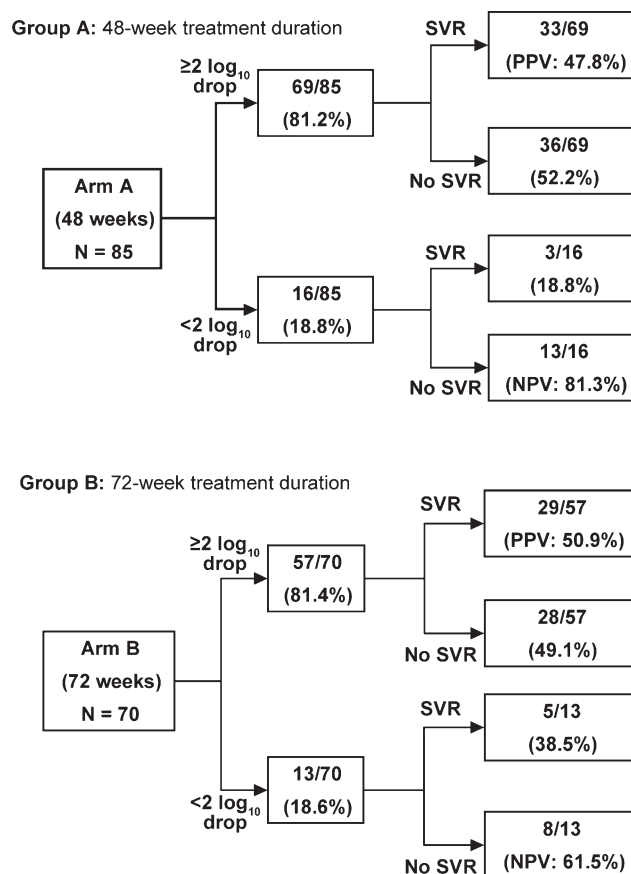


Fig. 3. Positive predictive value (PPV) and negative predictive value (NPV) of change in HCV RNA levels at week 8 in slow responders treated for 48 or 72 weeks. Week 8 HCV RNA analyses were not available for all slow responders.

Table 2. Adverse Events Occurring in at Least 20% of Patients in Any Treatment Arm

Adverse Event, n (%)	Group A (n = 86): 48 Weeks of Treatment	Group B (n = 73): 72 Weeks of Treatment	Group C (n = 816): cEVR, 48 Weeks of Treatment
At least one	83 (96.5)	71 (97.3)	792 (97.1)
Influenza-like illness	36 (41.9)	34 (46.6)	347 (42.5)
Asthenia	28 (32.6)	22 (30.1)	231 (28.3)
Headache	26 (30.2)	21 (28.8)	254 (31.1)
Alopecia	27 (31.4)	20 (27.4)	222 (27.2)
Fatigue	24 (27.9)	18 (24.7)	202 (24.8)
Myalgia	22 (25.6)	12 (16.4)	162 (19.9)
Pyrexia	21 (24.4)	18 (24.7)	245 (30.0)
Pruritus	20 (23.3)	12 (16.4)	176 (21.6)
Neutropenia	18 (20.9)	16 (21.9)	175 (21.4)
Nausea	18 (20.9)	15 (20.5)	159 (19.5)
Treatment-related	82 (95.3)	69 (94.5)	787 (96.4)
Serious	6 (7.0)	6 (8.2)	57 (7.0)
Leading to early withdrawal	3 (3.5)	6 (8.2)	41 (5.0)

28% in the 48-week treatment arms. Essentially, these studies showed that extending treatment duration to 72 weeks was associated with lower relapse in patients treated with a suboptimal dose of RBV. These observations led many investigators to conclude incorrectly that a longer regimen was more effective than the standard 48-week regimen, a strategy which has been further encouraged through its adoption into treatment guidelines.¹²

In the present study, the higher rate of dropout in the 72-week treatment arm clearly contributed to end-of-treatment response rates, which were 12% lower in the 72-week treatment group compared with the 48-week treatment group. However, both the per-protocol and completers analyses of this large population also revealed similar SVR rates, confirming that relapse rates do not change significantly when treatment duration is increased from 48 weeks to 72 weeks and, therefore, overall rates of SVR also remain similar. It is noteworthy that the relapse rate of 32.7% observed in the 72-week treatment arm is comparable to the relapse rate of 31.0% reported by Ferenci et al.¹⁰ in the subgroup of patients with partial early virologic response at week 12 and undetectable HCV RNA at week 24 who were treated for 72 weeks.

The use of a 72-week treatment duration has been assessed in G1 patients with detectable HCV RNA at week 4. In one study, a fixed dose of RBV (800 mg/day) was used, resulting in a low SVR rate of 28% in patients treated for 48 weeks.⁷ In the second study, RBV dosing was adjusted according to body weight, resulting in SVR rates of 51% and 60% with 48 and 72 weeks of therapy, respectively.¹⁰ The patients selected for extended treatment duration in these two studies were a heterogeneous population who achieved a virologic response at various time points after week 4

and, because some of these patients would have achieved undetectable HCV RNA between weeks 4 and 12 of treatment, they cannot be regarded as true slow responders.

In contrast, the SUCCESS study was specifically designed to look at the clinically important group of slow responders who become HCV RNA negative between weeks 12 and 24 and for whom there are no current evidence-based recommendations to guide treatment duration. In particular, the SUCCESS study was not designed to evaluate extended treatment among patients who attain undetectable HCV RNA between weeks 4 and 12 but to evaluate this strategy among patients with a partial early virologic response, and thus avoiding the inclusion of patients with complete EVR, a population that clearly do not require 72 weeks of therapy. In total, 11% of patients had a slow virologic response and attained SVR rates of 43% or 48% when treated for 48 or 72 weeks, respectively. One study performed in the United States used the same definition for slow responders and included a weight-adjusted RBV schedule.¹¹ The majority of patients in this study were African American. A high proportion of patients attained slow virologic response (31%), 18% of whom attained an SVR when treated for 48 weeks, much lower than the SVR rate attained by slow responders in a large study performed in a similar population treated for 48 weeks (45%).⁴ In addition, the SVR rate of 38% for slow responders treated for 72 weeks was lower compared with results from the present study, which included predominantly white patients, suggesting that the discrepancies between these studies can be attributed largely to differing patient characteristics within study populations.

Our study shows for the first time that approximately 20% of slow responders attain a ≥ 2 -log HCV

RNA drop by week 4, a further 60% attain a similar response between weeks 4 and 8, and the remaining 20% attain this response between weeks 8 and 12. Predictive analyses suggest that absence of a 2-log drop in HCV RNA level at week 8 warrants prospective evaluation as a criterion for identifying patients who may be suitable for extended treatment duration. Approximately 80% of all slow responders had a ≥ 2 -log drop in viremia at week 8, and $\approx 50\%$ of these attained an SVR, irrespective of treatment duration (there was no benefit associated with extending treatment duration in this cohort). In contrast, $\approx 20\%$ of slow responders failed to attain a ≥ 2 -log drop at week 8; among this cohort, SVR rates were 19% with 48 weeks of treatment and 39% with 72 weeks of treatment. Although based on small patient numbers (and excluding those with body weight > 125 kg), these data indicate that patients with a < 2 -log decline at week 8 and undetectable HCV RNA at week 24 represent the group of patients who will benefit most from extended treatment.

In conclusion, SVR rates were similar among slow responders who received a standard dose of PEG-IFN alfa-2b and weight-based RBV for 48 or 72 weeks. Thus, current practice and recommendations regarding prolonged therapy in slow responders are not supported by the results of our study and consequently require re-evaluation. The adverse event profiles were also similar; however, the rates of discontinuation were higher for the 72-week regimen. A 48-week regimen of PEG-IFN alfa-2b and RBV should remain a standard of care for these patients.

Acknowledgment: Writing assistance was provided by T. Ibbotson, Ph.D., and C. Knight, Pharm.D. The SUCCESS study investigators: F. Berr, M. Gschwantler (Austria); J. Delwaide, F. Nevens (Belgium); F. Anderson, M. Bilodeau, S. Feinman, N. Hilzenrat, K. Kaita, M. Levstik, S. Shafran, F. Wong, E. Yoshida (Canada); V. Hejda, T. Krechler, J. Sperl, P. Urbanek (Czech Republic); M. Buhl, C. Pedersen, H. Ring-Larsen (Denmark); M. Farkkila (Finland); D. Botta-Fridlundg, M. Bourliere, P. Cacoub, D. Guyader, C. Hezode, D. Larrey, P. Mathurin, D. Ouzan, A. Tran, C. Trepo, J.-P. Vinel, J.-P. Zarski (France); J. Arnold, T. Berg, P. Buggisch, J. Encke, C. Gelbmann, G. Gerken, T. Goeser, R. Gunther, H. Klinker, S. Mauss, J. Rasenack, S. Rossol, M. Singer, G. Teuber, K. Wiedmann, R. Zachoval (Germany); H. Bassaris, D. Dimitroulopoulos, J. Koskinas, S. Manolakopoulos, M. Raptopoulou-Gigi (Greece); L. Dalmi, J. Gervain, V. Jancsik (Hungary); S. Bar-Meir, E. Melzer, A. Nimer, D. Shouval, E. Sikuler, E. Zuckerman (Israel); A. Craxi, G. Pinzello, M. Rizzetto (Italy); A. Irnuius, Z.

Sukys, J. Sumskiene (Lithuania); J. Florholmen, L. Karlsen (Norway); J. Cianciara, A. Gietka, A. Gladysz, W. Halota, J. Juszczak (Poland); L. Matos, R. Sarmiento e Castro, C. Valente (Portugal); F. Rodriguez-Perez (Puerto Rico); V. Morozov, V. Rafalsky (Russia); J. Aguilar Reina, R. Barcena Marugan, J. Calleja, B. Dalmau Obrador, M. Garcia Bengochea, A. Lopez Morante, R. Moreno Otero, O. Nunez Martinez, J. Ortiz Seuma, J. Pedreira Andrade, F. Pons Romero, M. Rodriguez Garcia, J. Sanchez-Tapias, J. Such Ronda, J. Viver Pi-Suner, J. Zozaya Urmenata (Spain); O. Weiland, J. Westin (Sweden); A. Cerny, J.-J. Gonvers, M. Heim, B. Mullhaupt (Switzerland); H. Dubynska, O. Golubovska, N. Gubergrits, B. Herasun, D. Ipatova, N. Kharchenko, L. Moroz, V. Topolnytsky, Z. Vozianova (Ukraine); M. Cramp, S. Ryder (United Kingdom).

References

1. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-965.
2. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-982.
3. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon- $\alpha 2a$ and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-355.
4. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-593.
5. Mangia A, Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V, et al. Individualized treatment duration for hepatitis C genotype 1 patients: a randomized controlled trial. *HEPATOLOGY* 2008;47:43-50.
6. Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology* 2006;130:1086-1097.
7. Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006;131:451-460.
8. Buti M, Valdes A, Sanchez-Avila F, Esteban R, Lurie Y. Extending combination therapy with peginterferon alfa-2b plus ribavirin for genotype 1 chronic hepatitis C late responders: a report of 9 cases. *HEPATOLOGY* 2003;37:1226-1227.
9. Brouwer JT, Nevens F, Bekkering FC, Bourgeois N, Van Vlierberghe H, Weegink CJ, et al. Reduction of relapse rates by 18-month treatment in chronic hepatitis C. A Benelux randomized trial in 300 patients. *J Hepatol* 2004;40:689-695.
10. Ferenci P, Laferl H, Scherzer TM, Maieron A, Hofer H, Stauber R, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C type 1 and 4 patients with slow virological response. *Gastroenterology* 2010;138:503-512.e1.
11. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *HEPATOLOGY* 2007;46:1688-1694.
12. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *HEPATOLOGY* 2009;49:1335-1374.