

HCV RNA Negativity After 12 Weeks of Therapy Is the Best Predictor of Sustained Viral Response (SVR) in the Re-treatment of Previous Interferon alfa/Ribavirin Nonresponders (NR): Results From the EPIC³ Program

T. Poynard,¹ E. Schiff,² R. Terg,³ R. Moreno Otero,⁴ S. Flamm,⁵ W. Schmidt,⁶ T. Berg,⁷ F. Goncales Jr.,⁸ J. Heathcote,⁹ M. Diago,¹⁰ T. McGarrity,¹¹ A. Maieron,¹² J. Reichen,¹³ H. Tanno,¹⁴ C. Brandao,¹⁵ J. McHutchison,¹⁶ M. Silva,¹⁷ P. Bedossa,¹⁸ W. Deng,¹⁹ P. Mukhopadhyay,¹⁹ L. Griffel,¹⁹ M. Burroughs,¹⁹ C. Brass,¹⁹ J. K Albrecht¹⁹

¹Hopital Pitie-Salpetriere, Paris, France; ²University of Miami, Miami, Florida; ³Hospital Municipal de Gastroenterologia Dr. Bonorino Udaondo, Buenos Aires, Argentina; ⁴Hospital Universitario de la Princesa, Madrid, Spain; ⁵Northwestern University, Chicago, Illinois; ⁶VA Medical Center, Iowa City, Iowa; ⁷Universitätsklinik Charite, Campus Virchow Klinikum, Berlin, Germany; ⁸Hospital das Clinicas da Unicamp Cidade Universitaria Zefirina Vaz, Campinas-SP, Brazil; ⁹University Health Network, Toronto, Ontario, Canada; ¹⁰Hospital General Universitario de Valencia, Valencia, Spain; ¹¹Milton S. Hershey Medical Center, Hershey, Pennsylvania; ¹²Elisabethinen Hospital Linz, Linz, Austria; ¹³Institut Fuer Klinische Pharmakologie, Bern, Switzerland; ¹⁴Hospital Provincial Del Centenario, Rosario, Argentina; ¹⁵Brazil Hospital Unversitario Gaffree and Guinle, Rio de Janeiro, Brazil; ¹⁶McHutchison, Duke University Medical Center, Durham, North Carolina; ¹⁷Austral University Hospital, Buenos Aires, Argentina; ¹⁸Hopital de Bicetre, Paris, France; ¹⁹Schering-Plough Research Institute, Kenilworth, New Jersey

Abstract*

Introduction: The EPIC³ program includes a large, prospective, controlled trial designed to assess the safety and efficacy of re-treatment with peginterferon alfa-2b (PEG) and ribavirin (RBV) in subjects who have failed previous treatment with any interferon alfa plus ribavirin (IR), including those that had failed PEG/RBV or peginterferon alfa-2a/RBV. We have previously reported a surprisingly high SVR in these patients, especially those with an early viral response.

Aim: To define early viral response at week 12 as a predictor of SVR in these patients.

Methods: HCV NRs or those that had relapsed after previous treatment with IR who have significant fibrosis (METAVIR F2-F4) received PegIntron[®] 1.5 microgram/kg subcutaneously once weekly plus Rebetol 800-1400 mg/day for up to 48 weeks. All patients had pre-treatment biopsies scored by a single reviewer using METAVIR criteria. Plasma HCV-RNA was determined at weeks 12, 24 and 48 of therapy and FU 12 and 24 using a quantitative TaqMan[®] assay (SPRI; sensitivity 29 IU/mL). Genotype was determined by sequencing PCR product.

Results: Of the first 1354 patients treated in the combination therapy trial, 23% achieved SVR. Of those who attained $\geq 2 \log_{10}$ decrease in viral load at week 12, 37% achieved SVR; 56% of those who were HCV-RNA (-), but only 6% of those who attained a 2 log decrease in HCV-RNA but remained HCV-RNA positive. Of this latter group, 17% of subjects with very low viral load at TW12 (≤ 100 IU) achieved SVR compared to 5% of those with residual viral load of >100-250 IU, and 0 in those with HCV-RNA >750.

Conclusions: SVR is strongly correlated with a negative HCV-RNA or HCV-RNA near the lower limit of detection at week 12, but is extremely low in those with HCV-RNA >100 IU/mL. This data suggests that undetectable viral load at week 12 (<29 IU/mL) best defines a robust EVR that predicts SVR for previous IR treatment failures re-treated with PEG-Intron plus WBD ribavirin.

*Poster presents data updated since abstract submission.

Background

- Current projections suggest that by the year 2010, treatment-naïve patients with chronic hepatitis C will be replaced largely by patients who were nonresponsive to available therapies or who were ineligible to receive therapy because of advanced disease.
- There are no approved therapeutic options for patients who do not respond to combination therapy of pegylated interferon (PEG-IFN) alfa and ribavirin (RBV).
- Ability to predict efficacy of re-treatment of patients who were nonresponsive to or who relapsed after any IFN alfa plus RBV therapy would assist clinicians in managing these patients.
- Early virologic response (EVR) for treatment-naïve patients is currently defined as undetectable hepatitis C virus (HCV) RNA or a $\geq 2 \log_{10}$ decrease in HCV RNA at week 12 of therapy.¹
- The EPIC³ program is a large, prospective, international trial designed to assess the efficacy and safety of re-treatment of nonresponders and relapsers to IFN plus RBV therapy by use of PEG-IFN alfa-2b (PegIntron[®]) plus RBV.
 - Based on previous EPIC² results,² EVR is defined in nonresponders and relapsers as undetectable HCV RNA at week 12 of therapy.
 - Preliminary results from the first 575 enrolled patients showed that re-treatment of nonresponders or relapsers with significant fibrosis with PEG-IFN alfa plus weight-based RBV yielded sustained virologic response (SVR) rates of 21%.²
 - 38% of patients with an EVR, defined as a $\geq 2 \log_{10}$ decrease in HCV RNA at week 12, attained an SVR.
 - 57% of patients with undetectable HCV RNA (<29 IU/mL) at treatment week 12 attained an SVR.

Aim

- To further characterize EVR at week 12 of PEG-IFN alfa-2b plus RBV treatment as a predictor of SVR in previous nonresponders and relapsers to any IFN alfa plus RBV therapy.

Methods

Study Design

- Global, multicenter, open-label, single-arm, prospective study (Figure 1).

Patients

- Adult patients with chronic hepatitis C who had compensated liver disease and moderate to advanced hepatic fibrosis (METAVIR F2, F3, or F4) and who did not respond to or who relapsed after previous treatment with any IFN alfa in combination with RBV were enrolled.
 - Nonresponders to prior treatment were defined as patients with detectable HCV RNA after a minimum of 12 weeks of treatment with IFN alfa plus RBV; relapsers were defined as patients who had undetectable HCV RNA at the end of treatment with IFN alfa plus RBV but who subsequently had detectable HCV RNA.
 - Patients receiving their first dose of study medication on or before April 1, 2004 were included in this analysis.
 - Additional major inclusion criteria were as follows:
 - No history of IFN alfa-based therapy for 6 months prior to study entry.
 - Evidence of fibrosis by liver biopsy (METAVIR F2, F3, or F4) as read by a central pathologist.

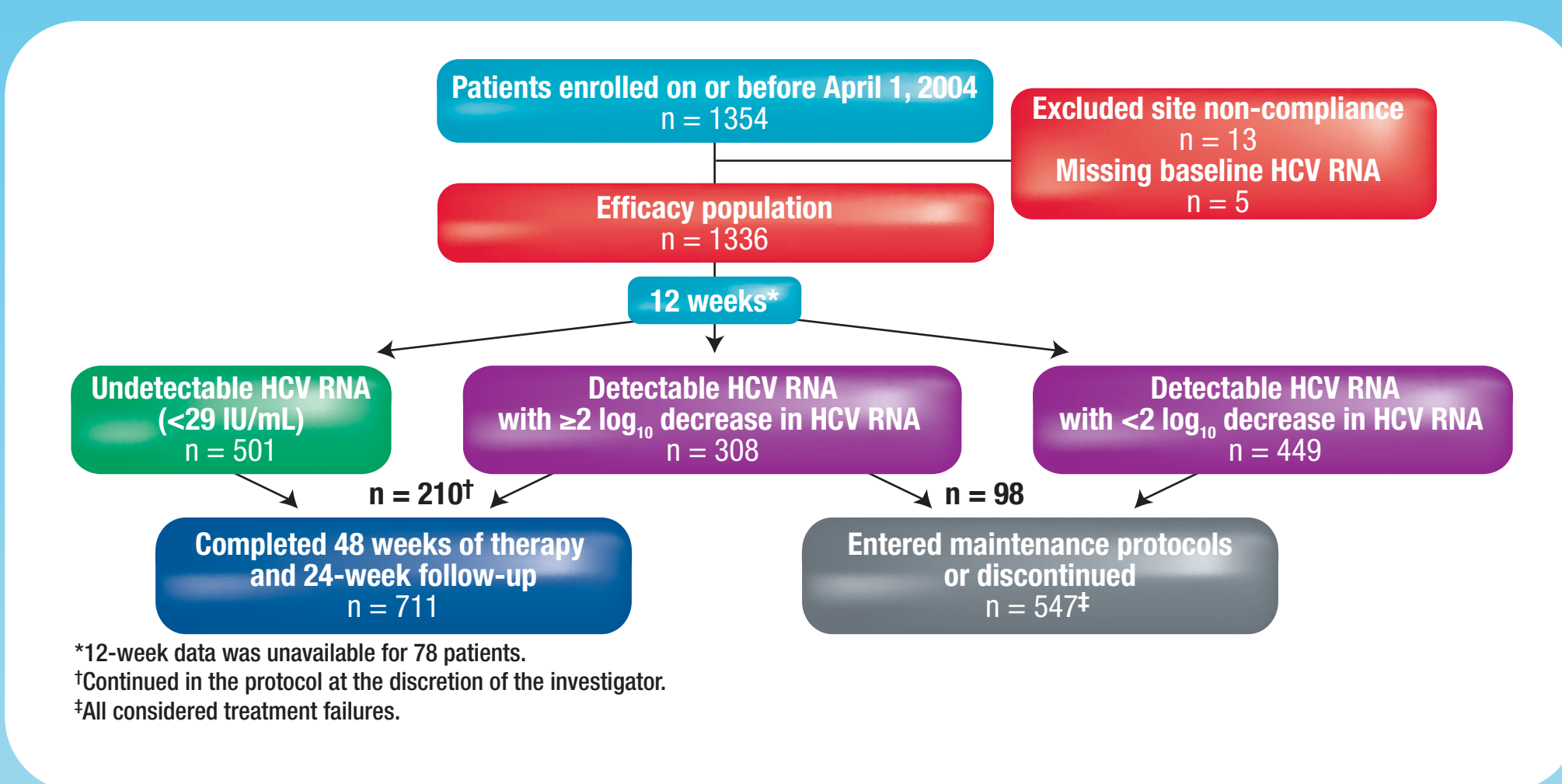


Figure 1. Patient flow

- Patients were excluded who had other causes of liver disease, coinfection with HIV or hepatitis B virus, evidence of decompensated liver disease, or history of hepatocellular carcinoma.
- The efficacy population (n = 1336; Figure 1; red box) was defined as all patients who received at least 1 dose of drug and who were not from sites that were excluded because of compliance issues.
- The 48-week treatment population (n = 711; Figure 1; dark blue box) was defined as all patients for whom 12-week data were available and who completed 48 weeks of therapy and follow-up at 24 weeks post-treatment.
- Treatment failures (Figure 1; grey box) were defined as patients who enrolled in the maintenance protocols because of lack of virologic response at week 12, patients who had a virologic response at week 12 but not an SVR, or patients who discontinued for any reason.
- HCV RNA levels <29 IU/mL (Figure 1; green box) were considered “undetectable.”

Treatment

- All patients received PEG-IFN alfa-2b (1.5 µg/kg/wk) plus weight-based RBV (800-1400 mg/d; Table 1).
 - Patients in the 48-week treatment group received drug for 48 weeks. This included all patients who had undetectable HCV RNA at week 12 and those who had $\geq 2 \log_{10}$ decrease in HCV RNA at week 12 and received a protocol deviation based on the investigator request to continue treatment (Figure 1).
 - Patients who had detectable HCV RNA at week 12 and did not receive a protocol deviation were assigned to one of the maintenance studies based on fibrosis score. Those who did not wish to continue were discontinued from the study (Figure 1).

Table 1. Ribavirin Dosing

Weight, kg	Ribavirin Dose, mg/d
40-65	800
>65-85	1000
>85-105	1200
>105	1400

Study Outcomes

- The primary end point of the study was SVR, defined as undetectable plasma HCV RNA at the end of 24 weeks of follow-up.
 - Plasma HCV RNA was determined at weeks 12, 24, and 48 of therapy and at 12 and 24 weeks after treatment cessation using a quantitative TaqMan[®] assay (Applied Biosystems, Foster City, CA; SPRI; sensitivity 29 IU/mL).

Results

Demographics

- A total of 1354 patients received the first dose of study medication on or before April 1, 2004 (Figure 1).
- Patient demographic and disease characteristics for the safety population (n = 1341) are presented in Table 2.
 - Most patients were Caucasian males with genotype 1 HCV.
 - Most patients were treated previously with standard IFN alfa plus RBV and were nonresponders to this previous treatment.

Table 2. Patient Characteristics of the Safety Population

	All Patients* n = 1341	METAVIR Score			
		F2 n = 356	F3 n = 417	F4 n = 564	
Male, n (%)	950 (71)	259 (73)	296 (71)	392 (70)	
Caucasian, n (%)	1130 (84)	301 (85)	339 (81)	487 (86)	
Mean age, y	49.0	46.9	48.9	50.5	
Mean weight, kg	80.7	79.2	80.0	81.9	
Genotype, n (%)					
1	1075 (80)	284 (80)	327 (78)	461 (82)	
2/3	206 (15)	55 (15)	67 (16)	84 (15)	
4	48 (4)	13 (4)	18 (4)	17 (3)	
Missing	12 (1)	4 (1)	5 (1)	2 (<1)	
Viral load, n (%)					
$\leq 600,000$ IU/mL	598 (45)	160 (45)	176 (42)	260 (46)	
>600,000 IU/mL	739 (55)	195 (55)	241 (58)	302 (54)	
Missing	4 (<1)	1 (<1)	0	2 (<1)	
Previous combination therapy, n (%)					
IFN alfa + RBV	1033 (77)	289 (81)	324 (78)	417 (74)	
PEG-IFN alfa-2b + RBV	208 (16)	43 (12)	70 (17)	95 (17)	
PEG-IFN alfa-2a + RBV	92 (7)	24 (7)	22 (5)	46 (8)	
No combination therapy	8 (1)	0	1 (<1)	6 (1)	
Previous response, n (%)					
Nonresponder	856 (64)	220 (62)	267 (64)	366 (65)	
Relapser	326 (24)	98 (28)	100 (24)	127 (23)	
Treatment failure [†]	159 (12)	38 (11)	50 (12)	71 (13)	
Mean METAVIR score					
Activity	1.1	1.0	1.1	1.1	
Fibrosis	3.2	2.0	3.0	4.0	

*Includes 2 patients with METAVIR scores of F1 and 2 patients with missing fibrosis scores.

[†]Documentation of virology was not adequate during prior therapy to allow for patient categorization as nonresponder or relapser.

IFN = interferon; PEG-IFN = pegylated IFN; RBV = ribavirin.

Virologic Response Rates

- Overall, an SVR was attained by 23% of the efficacy population.
- 501 patients (38% of the efficacy population) had undetectable HCV RNA at week 12, and 553 patients (41% of the efficacy population) had undetectable HCV RNA at the end of treatment.

Virologic Response at Treatment Week 12 as a Predictor of SVR

- At week 12, undetectable HCV RNA was a more reliable predictor of SVR than $\geq 2 \log_{10}$ decreases in HCV RNA (Figure 2; Table 3).
- SVR rates were highest among patients with undetectable (<29 IU/mL) HCV RNA (56%; Figure 3) at week 12.
- Patients with HCV RNA levels of 29 IU/mL to 100 IU/mL at week 12 achieved higher SVR rates than those with >100 IU/mL HCV RNA levels; however, these rates were considerably lower than those among patients with levels ≤ 29 IU/mL at week 12.
- SVR rates were very low among patients with HCV RNA levels >100 IU/mL to 750 IU/mL at week 12.
- No patient with HCV RNA levels >750 IU/mL at week 12 attained an SVR.

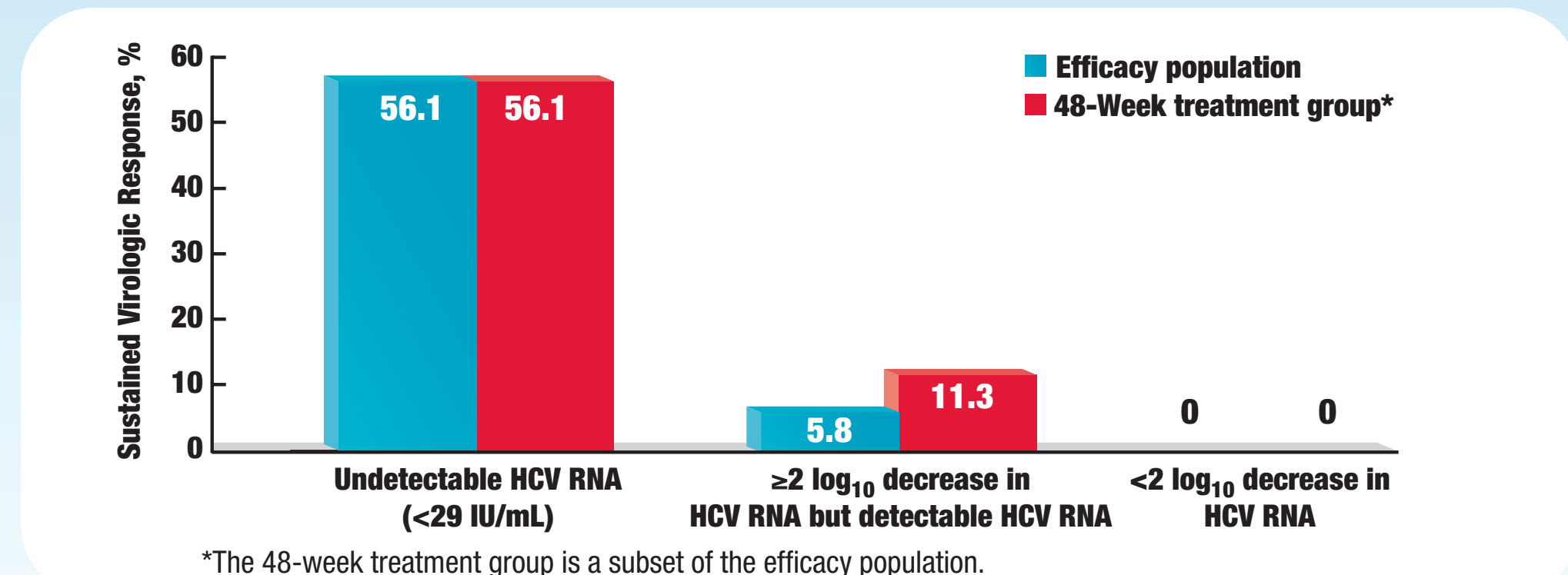


Figure 2. Sustained virologic response rates according to reduction in HCV RNA levels from baseline at week 12

Table 3. Sustained Virologic Response (SVR) Rates According to Virologic Response at Week 12

Virologic Response at Week 12	SVR, %
Undetectable HCV RNA (<29 IU/mL)	56.1
HCV RNA 29-100 IU/mL	16.9
$\geq 2 \log_{10}$ reduction in HCV RNA, but detectable HCV RNA	5.8
<2 log ₁₀ reduction in HCV RNA	0.0

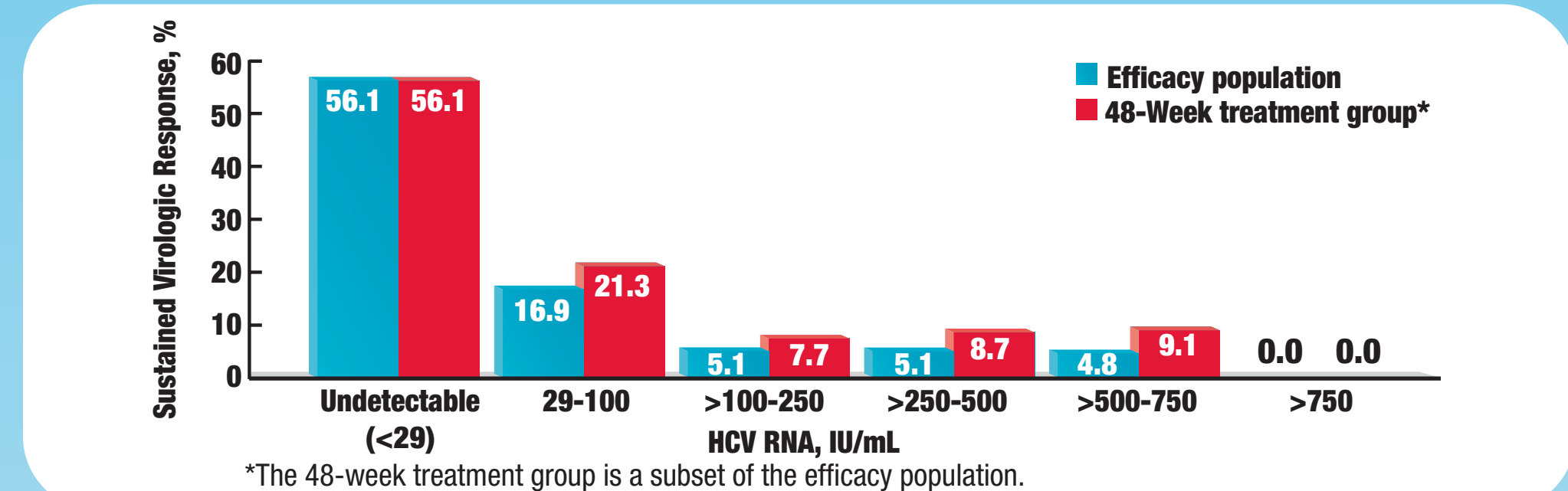


Figure 3. Sustained virologic response rates according to absolute HCV RNA levels at week 12

Conclusions

- Patients who do not respond or relapse after treatment with any IFN alfa plus RBV therapy can achieve SVR rates up to 56% if they reach viral negativity at week 12 of treatment with PEG-IFN alfa-2b plus RBV.
- Undetectable HCV RNA (<29 IU/mL) at week 12 is more predictive of an SVR than $\geq 2 \log_{10}$ reduction in HCV RNA at week 12 in patients undergoing re-treatment for chronic hepatitis C. SVR is extremely low in patients with HCV RNA >100 IU/mL at week 12.
- Undetectable HCV RNA at week 12 (<29 IU/mL) of PEG-IFN alfa-2b plus RBV treatment is a valuable tool to predict SVR among patients who failed with previous INF-based therapy.

Acknowledgments

J Aguilera Reina, Hospital Universitario Virgen del Rocío, Sevilla, Spain; A Alberti, Azienda Ospedaliera di Padova, Italy; F Anderson, The Liver and Intestinal Research Centre, Vancouver, Canada; L Balart, Louisiana State University Trials Office, Baton Rouge, LA, US; K Barange, C.H.U. de Toulouse, Hôpital de Purpan, France; H Bodenheimer, Beth Israel Medical Center, NY, US; M Bourliere, Hôpital Saint Joseph, Marseille, France; C Brandao, Hospital Unversitario Gaffree & Guinle, Rio de Janeiro, Brazil; J-P Bronowicki, C.H.U. de Nancy, Hôpital de Brabois Adultes, Vandœuvre les Nancy, France; H Brunner, Laizh Hospital of Vienna, Austria; W Burk, Heritage Medical Research Clinic/University of Calgary, Canada; J Caltija, Clínica Puerta de Hierro, Spain; F Carrilho, Hospital das Clinicas da FMUSP, Sao Paulo, Brazil; A Carvalho, Servico de Medicina III - HUC, Coimbra, Portugal; G Castellano, Hospital 12 de Octubre, Madrid, Spain; X Causse, C.H.R. d'Orleans, Hospital de la Source, France; W Cheng, Royal Perth Hospital, Australia; HSM Coelho, Hospital Universitario Clementino Fraga Filho, Rio de Janeiro, Brazil; L Colombo, Hospital Britanico, Buenos Aires, Argentina; M Colombo, Ospedale Maggiore-ROCS Policlinica, Milano, Italy; D Crawford, Princess Alexandra Hospital, Brisbane, Australia; A Craxi, Policlinico P. Giaccone, Palermo, Italy; J Curcanello, Hospital Interzonal General de Agudos; R Rodolfo, La Plata, Argentina; C Datz, Salzburg General Hospital, Austria; J Delvalde, CHU de Liege, Belgium; G Dusheiko, Royal Free Hospital, London, UK; R Enns, Burrell Medical Building, Vancouver, Canada; R Esteban-Mur, Hospital Vall d'Hebron, Barcelona, Spain; H Fairbrother, Hospital F. J. Muniz, Buenos Aires, Argentina; SV Feinman, Mount Sinai Hospital, Toronto, Canada; M Ferraz, Hospital Sao Paulo - Universidade Federal Sao Paulo - Focaccia, Instituto de Infectologia Emílio Ribas, Sao Paulo, Brazil; A Gostano, Hospital Italiano - Societa Italiana de Beneficenci, Buenos Aires, Argentina; J George, Westmead Hospital, Sydney, Australia; S Gordon, William Beaumont Hospital, Royal Oak, MI, US; KS Guffrond, Zedler Ledor Center, Edmonton, Canada; D Hausinger, Universitätsklinikum Duesseldorf, Germany; N Hilzenrat, Jewish General Hospital, Montreal, Canada; H Hinrichsen, Universitätsklinikum Kiel, Germany; V Horsmans, Hospital Saint Luc - ICL, Bruxelles, Belgium; R Hultcrantz, Karolinska University Hospital Solna, Stockholm, Sweden; I Jacobson, Weill Medical College of Cornell University, NY, US; G Joffrey, St Charles Gardner Hospital, Nideland, Australia; K Kato, Johns Ballier Research Centre, Winnipeg, Canada; P King, University of Missouri Hospital, Columbia, US; P Kwo, Indiana University School of Medicine, Indianapolis, IN, US; M-Y Lai, National Taiwan University Hospital, Taiwan; B Leggett, Royal Brisbane Hospital, Herston, Australia; L Lira, Hospital Sao Rafael, Salvador, Brazil; A Maieron, Elisabethinen Hospital Linz, Austria; E Manes, Hipokraton General Hospital of Athens, Greece; M Manis, Medizinische Hochschule Hannover, Germany; P Marcelin, A.P.H. Paris, Hospital Beaujon, Cligny, France; P Morotta, Lund Health Sciences Center - University Campus, CANADA; L Marsano, University of Louisville, HSU, KY, US; M Masad, Hospital Amal Carvalho, Jau, Brazil; AJ McQuillan, MetroHealth Medical Center, Cleveland, OH, US; L Molison, Fremantle Hospital, Australia; B Muellerhaupt, Universitätsklinik Zuerich, Switzerland; D Muzzillo, Hospital de Clinicas da UFPR, Curitiba, Brazil; M Ngu, Concord Hospital, Sydney, Australia; C Nieldera, St. Josef-Hospital Oberhausen, Germany; RPF Filho, Hospital Universitario Prof Egrad Santos, Salvador, Brazil; MP Pualy, Kaiser Permanente, Sacramento, CA, US; V Pehlekan, Queen Elizabeth II Health Sciences Center, Halifax, Canada; RP Alvarez, Hospital Central de Asturias, Oviedo, Spain; R Perriello, Ochsner Clinic Foundation, New Orleans, Louisiana, US; J Petersen, Universitätskrankehaus Hamburg, Germany; S Pianko, Alfred Hospital, Melbourne, Australia; A Piccotto, D.I.M.I. Universita' Di Genova, Italy; L Pinchuk, Sanatorio Municipal Julio A. Mendez, Buenos Aires, Argentina; R Pianos Vila, Hospital Germans Trias i Pujol, Barcelona, Spain; M Podda, Ospedale San Paolo, Milano, Italy; J-P. Poo-Ramirez, CIF BIOTEC/Hospital Medica Sur, D. F., Mexico; F Pordada, Cedars-Sinai Medical Center, LA, CA, US; R Poupon, A.P.H. Paris, Hôpital Saint Antoine, France; M Rames, Centro Medico Nacional SSST/OTR, D.F., Mexico; R Reinoldis, Caritas Center for Liver Diseases, Charlotte, NC, US; A Reymundo, Ponce Gastroenterology Research, Puerto Rico; M Rizzetto, Ospedale Molinette, Torino, Italy; H Rosa, Hospital Das Clinicas Da Universidade Federal De Go, Goiania, Brazil; W Rosenberg, Southampton General Hospital, UK; V Ruestgi, Metropolitan Research, Fairfax, VA, US; J Sanchez-Tapias, Hospital Clinic i Provincial, Barcelona, Spain; W Schmidt, Universitätsklinik St. Josef-Hospital, Medizinische, Bochum, Germany; W Schmidt, University of Iowa/VA Medical Center, Iowa City, IA, US; M Serra Destria, Hospital Clinico Universitario de Valencia, Spain; A D'Adda, University of Pittsburgh Medical Center, PA, US; K Sherman, University of Cincinnati, Ohio, US; W Sievert, Mönch Medical Centre, Clayton, Melbourne, Australia; M Silva, Hospital Universitario Austral, Pilar, Argentina; C Smith, Minnesota Gastroenterology, West Metro Division, Plymouth, MN, US; U Spengler, Rheinische Friedrich-Wilhelms-Universität Bonn, Germany; M Sulkowski, Johns Hopkins University, Baltimore, MD, US; R Teixeira, Faculdade de Medicina da UFMG, Belo Horizonte, MG, Brazil; D Toro, VA Medical Center, San Juan, Puerto Rico; E Torres, Unidad de Investigación de Gastroenterología, San Juan, Puerto Rico; A Tran, Hôpital de L'Arche 2, Nice, France; C Trovati, Hospices Civils de Lyon, Hotel Dieu, France; M Van Meir, St. Francis Medical Center, St. Francis Medical Center, Hospital da Arambá, Y. N. de Galia, Portugal; H Van Vlieterberg, Universitair ziekenhuis Gent, Belgium; A Varon, Fundacion Cardiolentini, Bogota, Colombia; E Villa, Policlinico Universitario di Modena, Italy; J Watson, John Hunter Hospital, Newcastle, Australia; F Wong, The Toronto General Hospital - University Health Net, Canada; Z Younsou, INOVA Fairfax Hospital, Falls Church, VA, US; R Zuchow, Klinikum Grosshadern der LMU Muenchen, Germany; S Zeuzem, Universitätsklinikum des Saarlandes - Klinik I, In, Homburg/Saar, Germany; AL Zignego, Azienda Ospedaliera Careggi, Firenze, Italy.

References

- Strader DB et al. *Hepatology*. 2004;39:1147-1171.
- Poynard T et al. *J Hepatol*. 2005;42(suppl 2):40-41.

Supported by Schering-Plough Research Institute