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Randomized trial of albinterferon alfa-2b every 4 weeks for chronic hepatitis C virus genotype 2/3

S. Pianko,[1] S. Zeuzem,[2] W.-L. Chuang,[3] G. R. Foster,[4] S. K. Sarin,[5] R. Flisiak,[6] C.-M. Lee,[7] P. Andreone,[8] T. Piratvisuth,[9] S. Shah,[10] A. Sood,[11] J. George,[12] M. Gould,[13] P. Komolmit,[14] S. Thongsawat,[15] T. Tanwandee,[16] J. Rasenack,[17] Y. Li,[18] M. Pang,[19] Y. Yin,[19] G. Feutren[20] and I. M. Jacobson[21] for the B2202 Study Team [1]*Monash Medical Centre and Monash University, Melbourne, Vic., Australia;* [2]*J.W. Goethe University Hospital, Frankfurt, Germany;* [3]*Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan;* [4]*Queen Mary's University of London, Blizard Institute of Cell and Molecular Science, London, UK;* [5]*Department of Hepatology, Institute of Liver and Biliary Sciences, G B Pant Hospital, Delhi, India;* [6]*Medical University of Bialystok, Bialystok, Poland;* [7]*Chang Gung Memorial Hospital–Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan;* [8]*Department of General Surgery and Organ Transplantation, Alma Mater Studiorum–Università di Bologna, Azienda Ospedaliero–Universitaria Policlinico S. Orsola–Malpighi, Bologna, Italy;* [9]*Department of Internal Medicine, NKC Institute of Gastroenterology and Hepatology, Songklanagarind Hospital, Prince of Songkla University, Hat Yai, Thailand;* [10]*Jaslok Hospital and Research Centre, Mumbai, India;* [11]*Department of Gastroenterology, Dayanand Medical College & Hospital, Ludhiana, Punjab, India;* [12]*Storr Liver Unit, Westmead Millennium Institute, University of Sydney and Westmead Hospital, Westmead, NSW, Australia;* [13]*Toronto Digestive Disease, Downsview, ON, Canada;* [14]*Department of Medicine, Gastroenterology Unit, Chulalongkorn University Hospital, Bangkok, Thailand;* [15]*Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand;* [16]*Siriraj Hospital, Bangkok, Thailand;* [17]*Albert Ludwigs University, Freiburg, Germany;* [18]*Novartis Institute for Biomedical Research, Cambridge, CA, USA;* [19]*Novartis Pharmaceuticals, East Hanover, NJ, USA;* [20]*Novartis Pharma AG, Basel, Switzerland; and* [21]*New York Presbyterian Hospital–Weill Cornell Medical College, New York City, NY, USA*

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SUMMARY. Albinterferon alfa-2b (albIFN) is a fusion protein of recombinant human albumin/recombinant interferon (IFN)-α-2b, with ~200-h half-life. Safety/efficacy of albIFN q4wk was evaluated in 391 treatment-naive patients with chronic hepatitis C virus (HCV) genotype 2/3. Patients were randomized 3:4:4:4 to one of four open-label treatment groups: pegylated IFN (Peg-IFN)-α-2a 180 μg qwk or albIFN 900, 1200 or 1500 μg q4wk, plus oral ribavirin 800 mg/day, for 24 weeks. Primary efficacy endpoint was sustained virologic response (SVR; HCV RNA <20 IU/mL 24 weeks post-treatment). SVR rates were as follows: 85%, 76%, 76% and 78% with Peg-IFNα-2a and albIFN 900, 1200 and 1500 μg, respectively (P = NS); corresponding rapid virologic response rates (HCV RNA <43 IU/mL at week 4) were as follows: 78%, 49% (P < 0.001), 60% (P = 0.01) and 71%. SVR rates were not influenced by interleukin 28B genotype, although rapid virologic response rates were greater with interleukin 28B CC (P = NS). Serious adverse event rates were as follows: 4%, 11%, 3% and 3% with Peg-IFNα-2a and albIFN 900, 1200 and 1500 μg, respectively. No increase in serious/severe respiratory events was noted with albIFN. Fewer absolute neutrophil count reductions <750/mm^3 occurred with albIFN (P = 0.03), leading to fewer IFN dose reductions. Haemoglobin reductions <10 g/dL were less frequent with albIFN 900 and 1200 μg *vs* 1500 μg and Peg-IFNα-2a (P = 0.02), leading to fewer ribavirin dose reductions. albIFN administered q4wk produced fewer haematologic reductions than Peg-IFNα-2a, but had numerically lower SVR rates (P = NS) in patients with chronic HCV genotype 2/3.

Keywords: albinterferon alfa-2b, hepatitis C virus, interferon, sustained virologic response.

INTRODUCTION

Hepatitis C virus (HCV) is endemic in most parts of the world, with an estimated overall prevalence of 3% (or 170 million infected individuals), and is a frequent cause of liver disease, including liver failure and hepatocellular carcinoma [1]. HCV genotypes (Gt) 2 and 3 represent 20–40% of chronic HCV infections in North America and Western Europe, and

Abbreviations: AE, adverse event; albIFN, albinterferon alfa-2b; ETR, end-of-treatment response; EVR, early virologic response; Gt, genotype; HCV, hepatitis C virus; IFN, interferon; *IL28B*, interleukin 28B; ITT, intention-to-treat; IVRS, interactive voice response system; LOD, limit of detection; LOQ, limit of quantitation; Peg-IFN, pegylated IFN; q2wk, once every 2 weeks; q4wk, once every 4 weeks; qwk, once every week; RBV, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response.

Correspondence: Stephen Pianko, MD, PhD, FRACP, Monash Medical Centre, 246 Clayton Rd, Clayton, Melbourne, Vic. 3145, Australia.
E-mail: spianko@geds.com.au

60% in Southeast Asia [2]. Twenty-four-week combination therapy with pegylated interferon (Peg-IFN)-α injected once weekly (qwk) plus daily oral ribavirin (RBV) has become the standard of care for treatment of chronic HCV Gt 2 or 3 [3]. Pegylated IFNα injections are, however, associated with postinjection symptoms such as chills, fever, myalgia, arthralgia, fatigue and headache, which often necessitate concomitant therapy with antipyretics and analgesics. In addition, weekly injections create a burden for the patient with respect to convenience, fear of self-injection and travel when the treatment needs to be administered at a healthcare centre. Fewer injections may, therefore, be an important factor in the decision to undergo treatment and in adherence to therapy.

Albinterferon alfa-2b (albIFN) is a fusion polypeptide of recombinant human albumin and recombinant IFNα-2b, with a half-life of ~8 days and IFNα-like pharmacodynamic properties [4]. A phase 2 dose-ranging study, in which patients with chronic HCV Gt 1 received two albIFN injections (200–1200 μg) 14 days apart, demonstrated that albIFN levels were consistently detectable 28 days after the second injection and antiviral activity was maintained with the higher dose [5]. Recent phase 3 studies of albIFN 900 and 1200 μg injected every 2 week (q2wk) in combination with RBV showed efficacy similar to Peg-IFNα-2a for the treatment of chronic HCV Gt 1 or 2/3 [6,7]. In the phase 3 studies, increased rates of pulmonary adverse events (AEs) were noted with albIFN, including interstitial lung disease, compared with those seen with Peg-IFNα. In this study, lower doses of albIFN were investigated, and respiratory assessments were performed prospectively to assess whether any respiratory signals were present when injection frequency was reduced. In addition, albIFN was investigated as a once-every-4-wk (q4wk) regimen with the aim of further reducing injection burden and improving treatment convenience over standard qwk therapy with Peg-IFNα.

METHODS

Study oversight

This study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The institutional review boards of participating centres approved the study protocol. All patients provided written informed consent. Novartis Pharma AG (Basel, Switzerland) and Human Genome Sciences, Inc. (Rockville, MD, USA) sponsored the study. Novartis was responsible for collection and statistical analysis of the data. A trial steering committee comprising study investigators provided input to the protocol and oversight of the conduct of the study, and an independent data-monitoring committee was responsible for ongoing review of safety data during the study. The authors had full access to the data, wrote this manuscript and take responsibility for the accuracy of the reported analysis.

Patient selection

Adult patients (aged ≥18 years) were enrolled in the study if they had chronic HCV Gt 2 or 3 and had not previously received IFNα therapy. Patients were excluded if they had decompensated liver disease or other causes of chronic liver disease, thrombocytopenia (<90 000 platelets/mm^3), neutropenia (<1500 neutrophils/mm^3), history of moderate–severe psychiatric disease, immunologically mediated disease, uncontrolled thyroid disease, clinical evidence of pre-existing interstitial or other severe lung diseases (by pulmonary function testing and chest X-rays at screening), co-infection with hepatitis B virus or HIV, a significant coexisting medical condition, or alcohol or drug dependence.

Study design

This phase 2b, randomized, multicentre, active-controlled, open-label, dose-ranging study was conducted at 53 centres in 10 countries (Australia, Canada, Germany, India, Italy, Poland, Spain, Taiwan, Thailand and UK) between October 2008 and May 2009 (ClinicalTrials.gov identifier NCT00759200). The median number of patients enrolled per site was 5 (range 1–33).

A centralized randomization assigned patients in a 3:4:4:4 ratio, in blocks of 15, to 1 of 4 treatment groups: active control Peg-IFNα-2a (PEGASYS; Hoffmann-La Roche Inc, Basel, Switzerland) 180 μg qwk (24 subcutaneous injections) and albIFN 900, 1200 and 1500 μg q4wk (six subcutaneous injections/group). The initial design included the option of evaluating albIFN 1800 μg q4wk (and additional Peg-IFNα-2a controls, leading to an overall 5:4:4:4:4 randomization) after an interim review of the 6-month data from the lower doses by the data-monitoring committee. This option was not pursued because of the anticipated absence of additional efficacy benefit from the highest albIFN dose, and therefore, only the three lower doses were investigated. All patients were to receive oral RBV 800 mg/day in two divided doses (RIBASPHERE; Three Rivers Pharmaceuticals, Warrendale, PA, USA). At baseline, all eligible patients were randomized using an interactive voice response system (IVRS). Investigators called the IVRS after confirming that patients fulfilled all the inclusion/exclusion criteria. The IVRS assigned randomization numbers to patients, which were used to assign patients to a treatment group. Randomization numbers were not communicated to callers and were generated using the following procedure to ensure that treatment assignment was unbiased: a patient randomization list was produced by the IVRS provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These

randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication randomization list was produced by Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study drugs. The randomization scheme for patients was reviewed and approved by a member of the Novartis Biostatistics Quality Assurance Group.

Randomization was stratified by HCV Gt (2 or 3) and pretreatment serum HCV RNA level (≤ or >800 000 IU/mL). Treatment duration was 24 weeks, with 24-week follow-up. The study protocol specified stepwise (≥1 level) dose reductions of albIFN (steps down to 1200, 900, 700 and 500 μg) and Peg-IFNα-2a (steps down to 135, 90 and 45 μg) to manage haematologic abnormalities and moderate–severe AEs. The use of haematopoietic growth factors was not permitted.

Blood samples for the interleukin 28B (*IL28B*) single-nucleotide polymorphism rs12979860 Gt were collected retrospectively following the description by Ge *et al.* [8] of an association between the *IL28B* Gt and response to IFN therapy. Patients had to provide additional written informed consent for this test, and samples were obtained in one-third of the study population (n = 117).

Efficacy assessments

The primary efficacy endpoint was sustained virologic response (SVR), defined as HCV RNA < limit of detection (LOD; 20 IU/mL) at 24 weeks after the end of therapy. Secondary efficacy endpoints were rapid virologic response at week 4 (RVR), defined as HCV RNA < limit of quantification (LOQ; 43 IU/mL); early virologic response at week 12 (EVR), defined as HCV RNA <LOQ or >2-log HCV RNA reduction; and end-of-treatment response (ETR), defined as HCV RNA <LOD at the end of treatment. Assessment of HCV RNA levels was accomplished using real-time polymerase chain reaction (CE-marked COBAS® AmpliPrep/COBAS TaqMan® HCV test; Roche Diagnostics, Basel, Switzerland).

Viral kinetics

Assessments of HCV RNA were conducted in all patients at baseline, weeks 1, 2, 4, 12 and 24 on treatment, and weeks 4, 12 and 24 post-treatment. Intensive viral kinetics were examined in a subset of 38 patients with samples taken postdose at 12 and 24 h, days 3 and 8 and weeks 2, 3, 4, 6, 8, 10 and 12. All samples were obtained predose on injection days.

Safety assessments

Safety was assessed by physical examination and laboratory tests during treatment and through 24 weeks after completion of therapy to document resolution of any ongoing AEs. Dose reductions of one or both drugs were permitted for clinically significant AEs or laboratory abnormalities. A single dose of albIFN or up to five doses of Peg-IFNα-2a could be withheld before discontinuation of the patient from the study. The severity of AEs was graded using the Division of Microbiology and Infectious Diseases toxicity rating scale [9].

Statistical methods

Because the primary objective of the study was to assess the safety and tolerability of the albIFN q4wk regimens, sample size was chosen based on the power to detect treatment-related AEs rather than statistical power for hypothesis testing. With 100 patients per albIFN treatment group, the probability of observing ≥1 AE with an underlying rate of 2% was >80%.

All analyses were performed in the intention-to-treat (ITT) population, defined as the subset of all randomized patients who received ≥1 dose of study agent. Adherence to IFN and RBV therapy was calculated as the total dose received/planned (based on 24 weeks of planned full-dose treatment) and expressed as a percentage. All statistical tests were two sided and performed at the 5% level of significance. All analyses were performed using SAS 9 statistical software (SAS Institute Inc., Cary, NC, USA). The SVR and on-treatment response rates for each treatment group, and the differences between each albIFN group and the Peg-IFNα-2a group were estimated with 95% confidence intervals. Statistical testing was performed using Pearson chi-square test (or Fisher's exact test when >20% of expected contingency table cell counts were <5). Safety was reported, and overall comparisons were made by treatment group.

RESULTS

Patient disposition and demographics

In all, 623 patients were screened, 391 were randomized, and 388 received ≥1 dose of study medication, constituting the ITT population (Fig. 1). Patient demographics and disease characteristics were similar among treatment groups (Table 1). About half of patients were enrolled in Asian countries, and most (72%) had HCV Gt 3. Using the rs12979860 tag single-nucleotide polymorphism, the *IL28B* Gt was recorded in 117 patients: 61 (52.1%) had the CC Gt, 52 (44.4%) had CT, and 4 (3.4%) had TT. Patients from Taiwan had a higher frequency of the *IL28B* CC Gt (28/31; 90.3%) than those from Western countries (33/86; 38.4%), a geographic distribution that may be reflected in the higher frequency of the *IL28B* CC Gt in patients with HCV Gt 2 (41/61; 67.2%) *vs* Gt 3 (20/56; 35.7%). This is a result of the increased frequency of Gt 2 in the Asian patients. Liver histology was not assessed in this study following standard treatment guidelines for the HCV Gt 2/3 population [3].

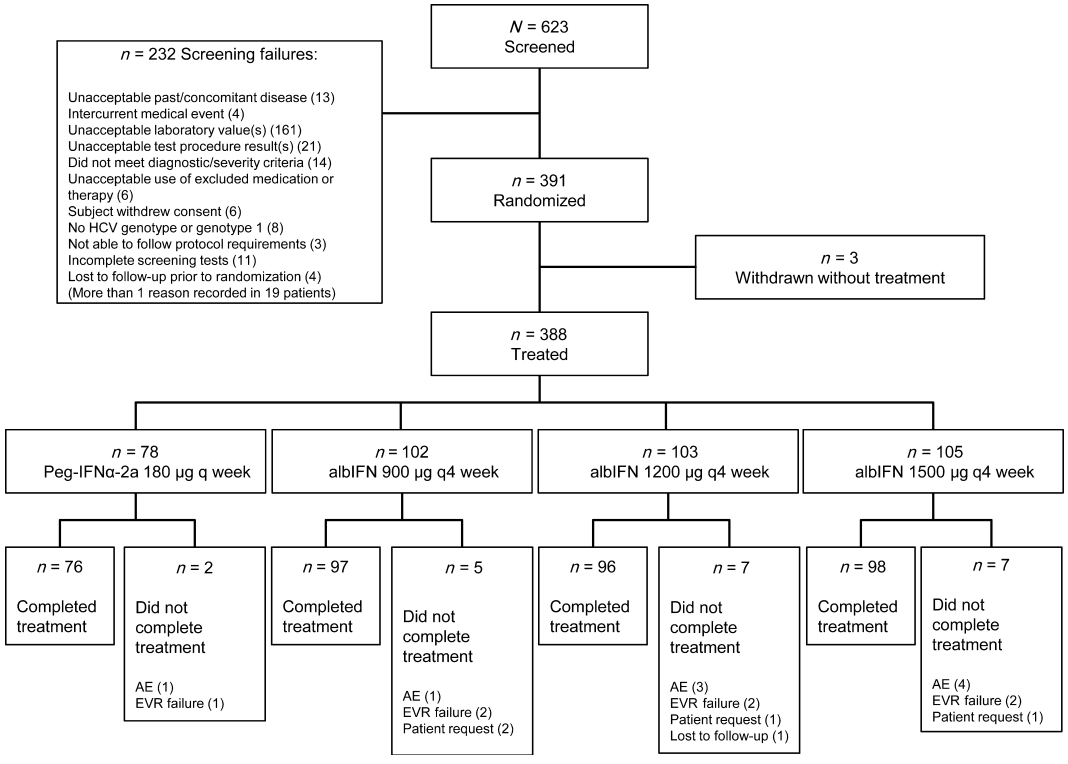

Fig. 1 Study disposition. AE, adverse event; albIFN, albinterferon alfa-2b; HCV, hepatitis C virus; Peg-IFNα-2a, pegylated interferon-α-2a; EVR, early virologic response at week 12.

Efficacy

The SVR rates in the ITT population were 84.6%, 75.5%, 75.7% and 78.1% with Peg-IFNα-2a 180 µg qwk and albIFN 900, 1200 and 1500 µg q4wk, respectively (P = NS; Fig. 2). Rapid virologic responses occurred in a dose-dependent fashion in the three albIFN groups, with lower rates than with Peg-IFNα-2a (49.0% [$P < 0.001$], 60.2% [$P = 0.01$] and 70.5% with albIFN 900, 1200 and 1500 µg, respectively, *vs* 78.2%). The EVR and ETR rates were high in all patients. Virologic breakthrough (HCV RNA levels >LOQ on treatment after having previously achieved levels <LOD) was observed in one patient each in the Peg-IFNα-2a and albIFN 1200-µg groups, but not in the other albIFN groups. Relapse rates ranged from 13.3% to 18.1%.

Viral kinetics

Viral load decline at week 2 was significantly greater with albIFN 1200 µg ($P = 0.003$) and 1500 µg ($P = 0.01$) than with Peg-IFNα-2a (Fig. 3). At week 4, all albIFN groups had lesser declines than did the Peg-IFNα-2a group, the difference reaching statistical significance with albIFN 900 µg ($P = 0.001$), reflecting the differences in RVR rates. Viral load changes between baseline and week 12, however, were similar, in line with EVR rates across all groups.

In the 38-patient subgroup with intensive viral kinetics, the pattern of viral load decline was comparable to that of the overall population between weeks 4 and 12. During the first 4 weeks, viral load decline was greater with Peg-IFNα-2a at weeks 2, 3 and 4 than with albIFN 900 µg. After the second albIFN 900-ug injection at week 4, viral suppression was similar to that with Peg-IFNα-2a and the other albIFN doses.

Baseline predictors of sustained virologic response

In general, SVR rates by patient subgroup reflected the differences between treatment arms observed in the overall population (Table S1). As expected, SVR rates were higher in younger patients and those with HCV Gt 2, baseline HCV RNA <800 000 IU/mL, low γ-glutamyl transpeptidase at baseline and lower body weight. In harder-to-treat patients with HCV Gt 3 and baseline HCV RNA >800 000 IU/mL, SVR rates (range 66–74%) were ~10% lower than that of the whole population.

Interleukin 28B genetic variation and virologic response

In the subset of 117 patients with *IL28B* genetic testing, the *IL28B* genetic variation did not affect baseline viral load: 72.1% of patients with the CC Gt had a baseline HCV RNA level >800 000 IU/mL *vs* 64.3% with a non-CC Gt

Table 1 Patient baseline characteristics

	Peg-IFNα-2a 180 μg qwk (n = 78)	albIFN 900 μg q4wk (n = 102)	albIFN 1200 μg q4wk (n = 103)	albIFN 1500 μg q4wk (n = 105)
Age				
Mean ± SD, years	43.3 (11.4)	42.2 (12.4)	43.2 (12.0)	41.3 (11.3)
≥45 years, *n* (%)	42 (53.8)	43 (42.2)	46 (44.7)	46 (43.8)
Race, *n* (%)				
Caucasian	36 (46.2)	46 (45.1)	41 (39.8)	51 (48.6)
Asian	39 (50.0)	53 (52.0)	60 (58.3)	50 (47.6)
Other	3 (3.9)	3 (2.9)	1 (2.0)	4 (3.8)
Ethnicity, *n* (%)				
Chinese: Taiwan	9 (11.5)	12 (11.8)	17 (16.5)	18 (17.1)
Indian: subcontinent	17 (21.8)	25 (24.5)	24 (23.3)	18 (17.1)
Other Asian: Thailand	13 (16.7)	16 (15.7)	19 (18.4)	14 (13.3)
Male sex, *n* (%)	50 (64.1)	66 (64.7)	65 (63.1)	57 (54.3)
Body wt ≥ 75 kg, *n* (%)	32 (41.0)	40 (39.2)	34 (33.0)	38 (36.2)
BMI ≥ 25 kg/m^2, *n* (%)*	44 (56.4)	52 (51.0)	38 (36.9)	44 (41.9)
HCV Gt, *n* (%)				
2	22 (28.2)	30 (29.4)	28 (27.2)	30 (28.6)
3	56 (71.8)	72 (70.6)	75 (72.8)	75 (71.4)
IL28B Gt				
CC	9/21 (42.9)	17/33 (51.5)	18/32 (56.3)	17/31 (54.8)
CT	11/21 (52.4)	16/33 (48.5)	13/32 (40.6)	12/31 (38.7)
TT	1/21 (4.8)	0/33 (0)	1/32 (3.1)	2/31 (6.5)
Mean disease duration ± SD, years	4.0 (5.39)	4.7 (5.64)	4.7 (5.32)	4.5 (4.70)
HCV RNA ≥800 000 IU/mL, *n* (%)	46 (59.0)	66 (64.7)	70 (68.0)	66 (62.9)
ALT > 1.5 × ULN, *n* (%)	51 (65.4)	61 (59.8)	55 (53.4)	59 (56.2)
GGT ≤ ULN, *n* (%)*	48 (61.5)	73 (71.6)	75 (72.8)	85 (81.0)

albIFN, albinterferon alfa-2b; ALT, alanine aminotransferase; BMI, body mass index; GGT, γ-glutamyl transpeptidase; Gt, genotype; HCV, hepatitis C virus; *IL28B*, interleukin 28B; Peg-IFNα-2a, pegylated interferon-α-2a; SD, standard deviation; ULN, upper limit of normal. *P < 0.05; 2-sided P-value for comparison of treatment groups obtained from Pearson chi-square test or Fisher's exact test.

(P = NS). There was no difference in overall SVR rates between patients with the CC Gt (50/61; 82.0%) and CT or TT Gt (44/56; 78.6%; P = NS), and no difference within treatment groups (Table 2). Virologic response rates did not differ between the 117 patients with *IL28B* genetic testing and the 271 who were not genotyped: 62.4% *vs* 64.2% for RVR and 80.3% *vs* 77.1% for SVR. The *IL28B* genetic variation did not demonstrate a consistent effect on RVR. Overall, RVR rates were 67.2% *vs* 57.1% in patients with *vs* without the CC Gt (P = NS). Within treatment groups, differences in RVR between patients with and without the CC Gt were not consistent and were limited by the small sample size. In multivariate analyses, the *IL28*B Gt was not identified as a significant factor of virologic response. Significant variables for RVR and SVR were viral load at baseline, HCV Gt and HCV disease duration, as well as albIFN 900-μg q4wk *vs* Peg-IFNα-2a 180-μg qwk treatment group for RVR only and patient age for SVR only (Table 3). Because of the low number of patients who did not achieve RVR and were also tested for the *IL28B* Gt (3 with Peg-IFNα-2a), it could not be determined whether the host *IL28B* Gt was a predictor of response in this patient subset, as previously reported [10].

On-treatment predictors of sustained virologic response

Rapid virologic response, as well as HCV RNA <LOD at week 2 or 4, had a high positive predictive value for SVR in all treatment groups (Table S2). The negative predictive value of RVR for SVR was, however, lower with albIFN 900 μg (40.4%) and 1200 μg (46.3%) than with albIFN 1500 μg (54.8%) or Peg-IFNα-2a (52.9%).

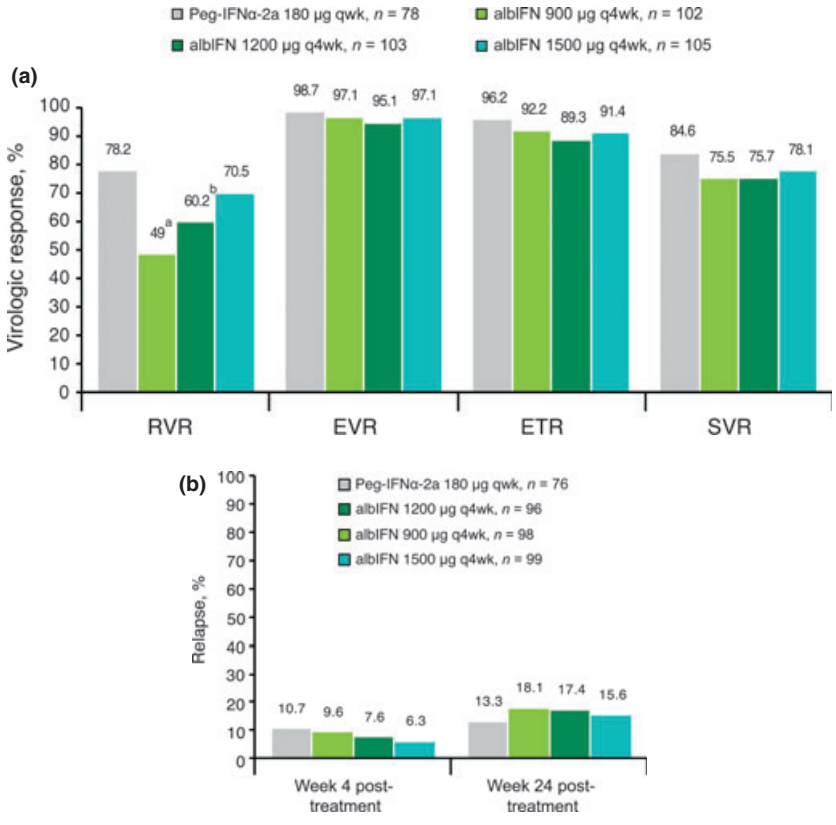

Fig. 2 Virologic response (a, intention-to-treat population) and relapse rates (b). Relapse defined as hepatitis C virus (HCV) < limit of detection (20 IU/mL) at end of treatment and becoming detectable at post-treatment visit. [a]P <0.001; [b]P = 0.01. albIFN, albinterferon alfa-2b; ETR, end-of-treatment response (HCV RNA < limit of detection); EVR, early virologic response at week 12 (HCV RNA < limit of quantification [43 IU/mL] or >2-log reduction); Peg-IFNα-2a, pegylated interferon-α-2a; RVR, rapid virologic response at week 4 (HCV RNA < limit of quantification); q4wk, once every 4 weeks; qwk, once every week; SVR, sustained virologic response 24 weeks after treatment (HCV RNA < limit of detection).

Adherence to therapy

Adherence was high in all treatment groups, with 85.9–95.1% of patients achieving ≥80% adherence to both IFN and RBV treatment (Table S3). Fewer patients had IFN dose reductions with all albIFN doses than with Peg-IFNα-2a 180 μg qwk, and fewer RBV dose reductions occurred with albIFN 900 and 1200 μg q4wk. The proportions of patients with ≥80% adherence to IFN were higher with albIFN (92.2–98.0%) than with Peg-IFNα-2a (88.5%; P = 0.05), although the proportions of patients with ≥80% adherence to RBV were similar in all treatment groups (89.5–95.1%). Overall, 3.8%, 5.8%, 5.8% and 6.7% of patients with Peg-IFNα-2a and albIFN 900, 1200 and 1500 μg, respectively, did not complete the study.

Adverse events

Adverse events leading to dose reduction or interruption of IFN or RBV were less frequent with albIFN 900 μg q4wk than with Peg-IFNα-2a 180 μg qwk (P = 0.03; Table 4). The numerically higher rate of patients with a serious AE in the albIFN 900-μg group (10.8%) than in the Peg-IFNα-2a (3.8%) and albIFN 1200-μg (2.9%) and 1500-μg (2.9%) groups was because of the high number of post-treatment serious AEs (six of 11; Table 5). One death was reported in the study with albIFN 1200 μg because of intentional narcotic overdose.

The rates of neutropenia <750 and <500/mm^3 were significantly lower with albIFN 900 μg q4wk than with Peg-IFNα-2a 180 μg qwk (5.0% *vs* 17.9% [P = 0.03] and 1.0% *vs* 9.0% [P = 0.01], respectively; Table 4); a similar trend was observed with the other albIFN doses. Anaemia (haemoglobin <10 g/dL) was also less frequent with albIFN 900 μg (11.9%) and 1200 μg (18.4%) than with Peg-IFNα-2a (25.6%; overall comparison P = 0.02). The reduced frequency of haematologic AEs led to fewer albIFN dose reductions.

The common AEs associated with albIFN treatment were those typically observed with IFNα (Table 4). The incidence rates of pyrexia and alopecia were higher with albIFN than with Peg-IFNα-2a. A dose–response relationship was noted in the albIFN groups for alopecia, but not for pyrexia. A trend for a lower incidence of AEs was seen with albIFN 900 μg q4wk *vs* Peg-IFNα-2a 180 μg qwk for fatigue and asthenia. Most other AEs had similar incidence rates across treatment groups. These common AEs were mostly mild in severity and rapidly reversible after treatment termination.

Pulmonary adverse events

Rates of cough were similar with Peg-IFNα-2a and albIFN 900 and 1200 μg, but higher with 1500 μg (Table 4). Dyspnoea was reported in 11.3% of patients and exertional dyspnoea in 7.0%, with no difference between treatment

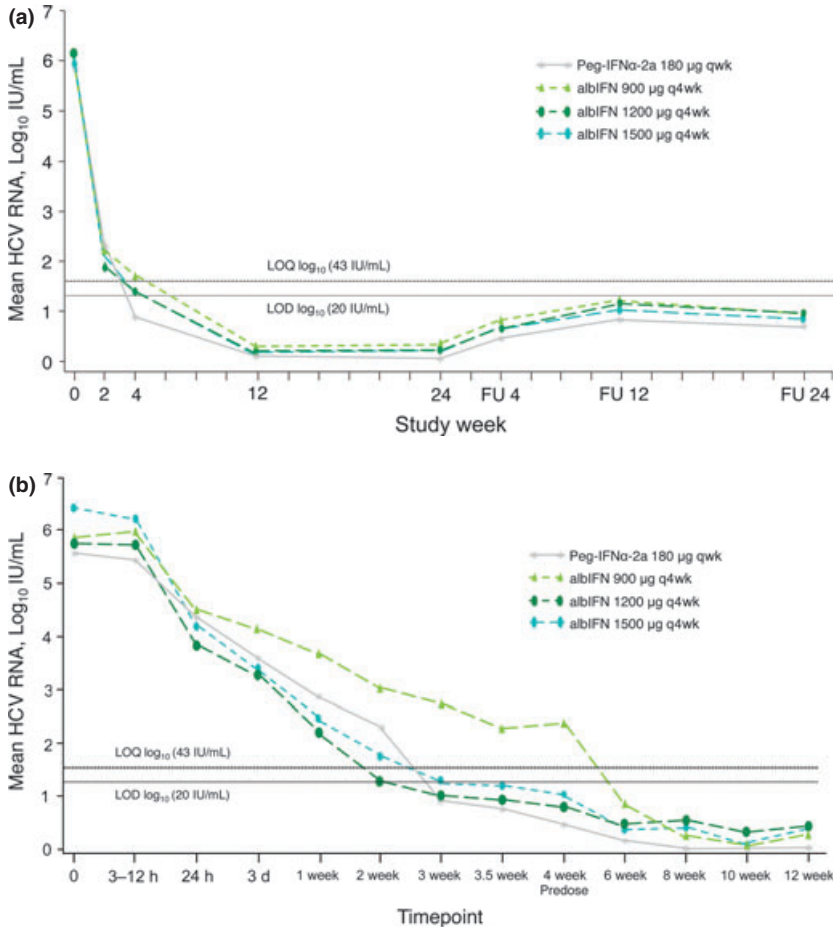

Fig. 3 Mean hepatitis C virus (HCV) RNA (log_{10} IU/mL) by week in (a) overall intention-to-treat population and (b) subset of 38 patients with intensive viral pharmacokinetics. albIFN, albinterferon alfa-2b; FU, follow-up; LOD, limit of detection; LOQ, limit of quantitation; Peg-IFNα-2a, pegylated interferon-α-2a; q4wk, once every 4 weeks; qwk, once every week.

Table 2 Interleukin 28B genetic variation and treatment response

	Peg-IFNα-2a 180 μg qwk (*n* = 21)	albIFN 900 μg q4wk (*n* = 33)	albIFN 1200 μg q4wk (*n* = 32)	albIFN 1500 μg q4wk (*n* = 31)	Total (*n* = 117)
RVR, *n* (%)					
CC	9/9 (100)	8/17 (47.1)	10/18 (55.6)	14/17 (82.4)	41/61 (67.2)
Non-CC	9/12 (75.0)	7/16 (43.8)	10/14 (71.4)	6/14 (42.9)	32/56 (57.1)
CT	8/11 (72.7)	7/16 (43.8)	9/13 (69.2)	5/12 (41.7)	29/52 (55.8)
TT	1/1 (100.0)	0/0 (0)	1/1 (100.0)	1/2 (50,0)	3/4 (75.0)
SVR, *n* (%)					
CC	8/9 (88.9)	13/17 (76.5)	14/18 (77.8)	15/17 (88.2)	50/61 (82.0)
Non-CC	10/12 (83.3)	14/16 (87.5)	9/14 (64.3)	11/14 (78.6)	44/56 (78.6)
CT	9/11 (81.8)	14/16 (87.5)	9/13 (69.2)	9/12 (75)	41/52 (78.8)
TT	1/1 (100)	0/0	0/1 (0.0)	2/2 (100)	3/4 (75.0)

albIFN, albinterferon alfa-2b; Peg-IFNα-2a, pegylated interferon-α-2a; RVR, rapid virologic response at week 4; SVR, sustained virologic response.

groups. Most of these common pulmonary AEs were of mild intensity, and no severe case was reported.

Four serious pulmonary AEs occurred with albIFN *vs* none with Peg-IFNα-2a. Three cases of pneumonia occurred with albIFN 900 μg – one of which led to treatment discontinuation – and one with 1200 μg, whereas none was reported with albIFN 1500 μg or Peg-IFNα-2a (Table 5). All cases of pneumonia resolved after appropriate therapy. One case of

Table 3 Multivariate analysis of association of RVR and SVR with treatment and baseline characteristics (n = 117)*

Parameter	Parameter estimate	SE	Odds ratio (95% CI)	*P*-value
RVR				
Intercept	3.2171	0.8741		<.001
Treatment: albIFN 1500 μg q4wk *vs* Peg-IFNα-2a 180 μg qwk	−1.3098	0.7912	0.27 (0.06, 1.27)	0.10
Treatment: albIFN 1200 μg q4wk *vs* Peg-IFNα-2a 180 μg qwk	−1.1045	0.7928	0.33 (0.07, 1.57)	0.16
Treatment: albIFN 900 μg q4wk *vs* Peg-IFNα-2a 180 μg qwk	−2.3517	0.7944	0.10 (0.02, 0.45)	0.003
HCV disease duration, years	−0.0777	0.0372	0.93 (0.86, 1.00)	0.04
Gt 2 *vs* 3	1.0923	0.4523	2.98 (1.23, 7.23)	0.02
Baseline HCV RNA ≥800 000 IU/mL	−1.8236	0.5677	0.16 (0.05, 0.49)	0.001
SVR				
Intercept	4.0705	0.9654		<0.001
Age ≥ *vs* <45 years	−2.0063	0.6751	0.13 (0.04, 0.50)	0.003
HCV disease duration, years	−0.0819	0.0406	0.92 (0.85, 1.00)	0.04
Gt 2 *vs* 3	1.7099	0.5897	5.53 (1.74, 17.56)	0.004
Baseline HCV RNA ≥800 000 IU/mL	−1.8314	0.8084	0.16 (0.03, 0.78)	0.02

albIFN, albinterferon alfa-2b; CI, confidence interval; Gt, genotype; HCV, hepatitis C virus; Peg-IFNα-2a, pegylated interferon-a-2a ; RVR, rapid virologic response at week 4; SE, standard error; SVR, sustained virologic response. Covariates tested in model: interleukin 28B single-nucleotide polymorphism rs12979860 Gt (CC, CT and TT); treatment group Peg-IFNα-2a 180 μg qwk and albIFN 900, 1200 and 1500 μg q4wk); age (≥ *vs* <45 years); sex (male *vs* female); HCV Gt 2 *vs* 3; body weight (≥ *vs* <75 kg); body mass index (≥ *vs* <25 kg/m^2); smoking status (current *vs* not current smoker); alcohol use (history *vs* no history of alcohol use); baseline alanine transaminase (> *vs* ≤1.5 × upper limit of normal); baseline γ-glutamyl transpeptidase (> *vs* ≤ upper limit of normal); region (Asian *vs* non-Asian); baseline HCV RNA (≥ *vs* <800 000 IU/mL); and HCV disease duration (years). *Subgroup with interleukin 28B genetic testing.

restrictive lung disease – reported at week 12 with albIFN 1500 μg – led to treatment discontinuation and reversed after the end of treatment.

DISCUSSION

High rates of on- and post-treatment virologic responses were observed in all treatment groups, although SVR rates were greater with Peg-IFNα-2a 180 μg qwk. The RVR rates were significantly lower with albIFN q4wk, particularly when comparing 900 and 1200 μg with Peg-IFNα-2a qwk; however, these differences resulted in smaller differences in SVR rates than may have been expected from the differences in RVR. The results obtained with albIFN q4wk showed similar EVR, ETR and SVR rates to those reported in the phase 3 ACHIEVE-2/3 trial with albIFN q2wk in patients with HCV Gt 2/3 [6]. In that study, however, patients treated with albIFN 900 μg q2wk achieved a similar RVR rate to that with Peg-IFNα-2a 180 μg qwk in comparison with the lower, dose-dependent rates observed with albIFN q4wk in the present study. In an earlier phase 2 study of albIFN q4wk in patients with HCV Gt 1, a similar pattern was noted, with lower RVR rates and similar, but numerically lower, SVR rates compared with Peg-IFNα-2a qwk [11].

The differential effect of albIFN on RVR compared with Peg-IFNα-2a may be explained by the pharmacokinetic profile that follows albIFN q4wk administration [5]. The lower plasma IFN exposure occurring at week 4 with albIFN q4wk *vs* albIFN q2wk or Peg-IFNα-2a qwk may delay achievement of HCV RNA negativity compared with more frequent injections. A delay in achieving initial HCV RNA undetectability results in a shorter overall duration of HCV RNA negativity on treatment, a factor associated with the likelihood of achieving an SVR [12]. The differential in RVR rates may, therefore, play some role in the SVR imbalance observed in this study. This finding raises questions regarding the intensity of the initial antiviral pressure obtained with a q4wk regimen, and the potential benefit of increasing the frequency of albIFN injections over the first 4 weeks of treatment to bolster the initial virologic response to equal that attained by the standard of care, followed by an albIFN q4wk regimen for the remainder of the treatment course. This hypothesis is supported by the higher week-2 virologic response rates, but lower RVR rates with albIFN q4wk in this study, which may be the result of attenuation of antiviral effect with the q4wk regimen. The impact of increasing RVR rates by increasing dosing in the first 4 weeks of therapy remains controversial. Studies in both Gt 1 and 2/3 have

Table 4 Adverse events and dose reductions or interruptions because of adverse events

	Peg-IFNα-2a 180 μg qwk (n = 78), n (%)	albIFN 900 μg q4wk (n = 102), n (%)	albIFN 1200 μg q4wk (n = 103), n (%)	albIFN 1500 μg q4wk (n = 105), n (%)	P-value*
≥1 AE	76 (97.4)	95 (93.1)	97 (94.2)	102 (97.1)	0.44
≥1 serious AE	3 (3.8)†	11 (10.8)†	3 (2.9)	3 (2.9)	0.03
≥1 severe AE	6 (7.7)	14 (13.7)	15 (14.6)	14 (13.3)	0.53
AE leading to IFN/RBV discontinuation	2 (2.6)	3 (2.9)	3 (2.9)	6 (5.7)	0.69
AE leading to dose reduction/ interruption	22 (28.2)	15 (14.7)	19 (18.4)	35 (33.3)	0.006
Death	0	0	1 (1.0)‡	0	0.73
Haematologic/total AEs (%)					
Neutrophil count					
<750/mm^3	14/78 (17.9)	5/101 (5.0)	14/103 (13.6)	9/105 (8.6)	0.03
<500/mm^3	7/78 (9.0)	1/101 (1.0)	2/103 (1.9)	1/105 (1.0)	0.009
Haemoglobin					
<10.0 g/dL	20/78 (25.6)	12/101 (11.9)	19/103 (18.4)	30/105 (28.6)	0.02
<8.5 g/dL	4/78 (5.1)	1/101 (1.0)	1/103 (1.0)	7/105 (6.7)	0.045
Platelets					
<50 000/mm^3	5/78 (6.4)	2/100 (2.0)	3/103 (2.9)	1/105 (1.0)	0.19
<25 000/mm^3	2/78 (2.6)	0/100	0/103	0/105	0.04
Common AEs (≥20% in any group)					
Alopecia	24 (30.8)	44 (43.1)	46 (44.7)	59 (56.2)	0.008
Pyrexia	26 (33.3)	49 (48.0)	46 (44.7)	49 (46.7)	0.20
Headache	29 (37.2)	34 (33.3)	44 (42.7)	37 (35.2)	0.54
Fatigue	29 (37.2)	33 (32.4)	35 (34.0)	30 (28.6)	0.66
Decreased appetite	21 (26.9)	28 (27.5)	29 (28.2)	26 (24.8)	0.95
Insomnia	21 (26.9)	26 (25.5)	27 (26.2)	26 (24.8)	0.99
Myalgia	20 (25.6)	24 (23.5)	27 (26.2)	23 (21.9)	0.93
Cough	16 (20.5)	24 (23.5)	22 (21.4)	31 (29.5)	0.44
Pruritus	19 (24.4)	25 (24.5)	17 (16.5)	23 (21.9)	0.49
Asthenia	15 (19.2)	13 (12.7)	24 (23.3)	21 (20.0)	0.27
Anaemia	17 (21.8)	13 (12.7)	13 (12.6)	29 (27.6)	0.01
Influenza-like illness	16 (20.5)	20 (19.6)	12 (11.7)	23 (21.9)	0.23
Nausea	14 (17.9)	16 (15.7)	22 (21.4)	17 (16.2)	0.71

AE, adverse event; albIFN, albinterferon alfa-2b; IFN, interferon; Peg-IFNα-2a, pegylated interferon-a-2a; RBV, ribavirin. *Two-sided P-value for comparison of treatment groups obtained from Pearson chi-square or Fisher's exact test for categorical data, or 1-way analysis of variance for continuous data. †Including 1 post-treatment serious AE in Peg-IFNα-2a 180-μg qwk group and six in albIFN 900-ug q4wk group; ‡Death by heroin overdose.

shown that RVR is the most powerful on-treatment predictor of response [13], although IFN induction studies have shown that enhanced initial on-treatment response rates may not improve SVR rates [14]. The impact of IFN-induced early virologic responses in the evolving era of direct-acting antiviral therapies associated with high RVR rates, such as boceprevir and telaprevir, remains to be elucidated [15,16].

The *IL28B* Gt was not a predictor of SVR in this chronic HCV Gt 2/3 cohort, in contrast to previous findings in patients with chronic HCV Gt 1 [8]. In two recent studies, the *IL28B* Gt was associated with RVR, but as in the present study, not with SVR [17,18]. In a separate study of Italian patients infected with HCV Gt 2/3, the *IL28B* Gt was a predictor of SVR in the 78 patients who failed to achieve an RVR [10]. In the present study, small patient numbers with available *IL28B* genotyping and failure to achieve an RVR precluded similar analysis. Larger patient cohorts stratified according to ethnicity are required to determine the influence of *IL28B* on HCV viral kinetics and virologic response following IFN/RBV-based therapy in Gt 2 and 3.

The overall incidence of AEs was high (>90%) and similar across treatment groups, with similar types of AEs. There was, however, a trend for more frequent severe AEs with albIFN, and the incidence of serious AEs was significantly higher with albIFN than with Peg-IFNα-2a. Unlike in previous albIFN studies, the rates of cough were the same across

Table 5 Serious adverse events

Peg-IFNα-2a 180 μg qwk	albIFN 900 μg q4wk	albIFN 1200 μg q4wk	albIFN 1500 μg q4wk
On treatment			
Bacterial sepsis	Pneumonia (n = 2)	Pneumonia	Lower limb fracture
Malaria	Pneumonia and neutropenia	Gastric ulcer haemorrhage	Restrictive lung disease
	Psoriasis	Heroin intoxication (fatal)	Pyrexia, anaemia
	Paternal exposure (pregnant partner)		
Post-treatment			
Thyroid cancer, thyrotoxicosis	Spinal cord infarction		
	Hypothyreosis		
	Colon cancer		
	Ketoacidosis		
	Suicidal ideation		
	Induced abortion		

albIFN, albinterferon alfa-2b; Peg-IFNα-2a, pegylated interferon-α-2a.

treatment groups [6,7]. As in the earlier trials, more respiratory infections and a case of restrictive lung disease were noted with albIFN treatment, although similar AEs are known to occur with Peg-IFNα, as well [19,20]. The persistent numeric imbalance in serious pulmonary AEs observed with albIFN *vs* Peg-IFNα across trials, however, creates concern regarding the pulmonary safety of the albIFN molecule. (Note: a full analysis of the changes in pulmonary function and respiratory effects of both albIFN and Peg-IFNα-2a in the present trial has been submitted for separate publication.) Alopecia and pyrexia rates were higher with albIFN *vs* Peg-IFNα-2a. The lower frequency of injections with albIFN q4wk was, however, associated with lower anaemia and neutropenia rates, and thus fewer IFN dose reductions than with Peg-IFNα-2a qwk. Overall, the 900-μg dose provided the best safety profile of the albIFN treatment groups. The improvement in haematologic profile appears to be related to the pharmacokinetic profile of albIFN q4wk, with the longer interval between injections allowing for recovery from IFN-induced bone marrow suppression. Although the albIFN doses used in this q4wk study were lower on a monthly average than the 900-μg q2wk dose used in the ACHIEVE-2/3 trial [6], pyrexia and alopecia rates remained higher than with Peg-IFNα-2a 180 μg qwk without a dose–response, suggesting that peak serum albIFN concentration may have driven these AEs rather than average concentration. Alopecia rates were higher in all albIFN groups than with Peg-IFNα-2a; whether alopecia rates were driven by peak serum concentration or were because of an intrinsic property or tissue distribution of the albIFN molecule is not clear.

While the focus of antiviral therapy for chronic HCV is projected by some to ultimately move away from IFN-based therapies, IFN-free regimens have not yet been developed beyond early trials [21]. Interferon may be required to diminish resistance to direct-acting antiviral agents, and an IFN platform with a reduced frequency of injections may be an important strategy if efficacy can be maintained with an improved AE profile. The present study demonstrates the ability to reduce the frequency of albIFN injections from q2wk to q4wk in a chronic HCV Gt 2/3 population with a small, statistically insignificant reduction in efficacy. It remains to be determined whether the combination of long-acting IFNs administered q4wk with direct-acting antiviral agents or intensification of IFN exposure in the first 4 weeks of therapy can overcome the reduction in efficacy seen in the present study.

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Lead investigators: *Australia*: Crawford D, Desmond P, George J, Pianko S, Sasadeusz J, Weltman M; *Canada*: Anderson F, Fournier C, Gould M, Swain M, Wong F, Yoshida E; *Germany*: Berg T, Buggisch P, Gerken G, Goeser T, Rasenack J, Zeuzem S (principal investigator); *India*: Habeeb A, Kapoor D, Kar P, Prabhakar B, Sarin S, Shah S, Sood A; *Italy*: Andreone P, Brunetto M, Craxi A, Mondelli M, Rizzetto M; *Poland*: Flisiak R, Jablkowski M; *Spain*: Andrade R, Barcena R, Buti M, Castellano D, Diago M, Perez R, Romero M, Sola R; *Taiwan*: Chang T, Chuang W, Kao J, Lee C; *Thailand*: Komolmit P, Piratvisuth T, Sukeepaisarnjaroen W, Tanwandee T, Thongsawat S; *United Kingdom*: Brown A, Cramp M, Foster GR, Mills P; *United States:* Jacobson, I, Bain V.

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The authors disclose the following: Stephen Pianko is a consultant for, advises and is on the speakers' bureaus of Human Genome Sciences (HGS), Novartis and Roche; Stefan Zeuzem is a consultant for HGS, Novartis and Roche and serves on the speakers bureaus of Novartis and Roche; Graham R. Foster has received funding from Novartis and Roche; Robert Flisiak has received research grants and is a consultant for HGS and Novartis; Teerha Piratvisuth is an advisor to, serves on the speakers bureaus of and has received research support from Novartis and Roche; Jacob George serves on the Australian Advisory Board of Novartis; Jens Rasenack has received research grants from HGS and Novartis; Yali Li, Maria Pang, Yanming Yin and Gilles Feutren are employees of and own stock in Novartis; and Ira M. Jacobson has received consulting fees and research funding from Novartis and HGS. No other potential conflicts of interest were reported.

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SUPPORTING INFORMATION

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

Table S1: Sustained virologic response by patient subgroup: ITT population

Table S2: On-treatment predictors of sustained virologic response.

Table S3: No. of patients with dose reductions/omissions and overall adherence to therapy.

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