Published in final edited form as:

Gastroenterology. 2010 October ; 139(4): 1267–1276. doi:10.1053/j.gastro.2010.06.062.

Albinterferon Alfa-2b Was Not Inferior to Pegylated Interferon- α in a Randomized Trial of Patients With Chronic Hepatitis C Virus Genotype 2 or 3

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Supplementary Material Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.06.062.

Clinicaltrials.gov ID NCT00411385.

The steering committee for the phase 3 program included authors Yves Benhamou, John G. McHutchison, and David R. Nelson, as well as Mark S. Sulkowski, MD (Johns Hopkins Infectious Disease Center for Viral Hepatitis, Baltimore, MD), and Stefan Zeuzem, MD (J.W. Goethe University Hospital, Frankfurt, Germany). Geoff Marx of BioScience Communications, New York, NY, provided editorial assistance supported by Human Genome Sciences and Novartis.

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Conflicts of interest The authors disclose the following: David Nelson has received research grants from Human Genome Sciences and Novartis, and is a consultant to Human Genome Sciences; Yves Benhamou is a consultant to Human Genome Sciences and Roche, and is a speaker for and has received research grants from Roche; Eric Lawitz has received research grants from Human Genome Sciences, Novartis, and Roche; Maribel Rodríguez-Torres has received research grants from Novartis and Roche, and is a consultant to Roche; Robert Flisiak has received research grants and is a consultant for Human Genome Sciences and Novartis; Jens Rasenack has received research grants from Human Genome Sciences and Novartis; Wiesław Kryczka has received research grants and is a consultant to Human Genome Sciences; Vincent Bain has received research grants from Human Genome Sciences and Novartis, and is a consultant to Human Genome Sciences; Stephen Pianko is a consultant for, advises, and is on the speakers' bureaus of Human Genome Sciences, Novartis, and Roche; Keyur Patel has received research grants from Human Genome Sciences and Novartis, and is a consultant to Novartis; Patrick W. Cronin, Erik Pulkstenis, and G. Mani Subramanian are employees of and own stock in Human Genome Sciences; John McHutchison has received research grants from and is a consultant to Human Genome Sciences, Novartis, and Roche.

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Abstract

BACKGROUND & AIMS—A phase 3 active-controlled study was conducted to assess the efficacy/safety of albinterferon alfa-2b (albIFN), a novel, long-acting, genetic fusion polypeptide of recombinant human albumin and interferon alfa-2b, in patients with chronic hepatitis C virus (HCV) genotype 2/3.

METHODS—In all, 933 patients were randomized to open-label subcutaneous treatment with pegylated interferon-alfa-2a (Peg-IFNalfa-2a) 180 µg/wk, or albIFN 900 or 1200 µg every 2 weeks for 24 weeks, each administered with oral ribavirin 800 mg/day. The primary end point of the study was sustained virologic response (SVR) (HCV-RNA level, <15 IU/mL at week 48). During the study, the data monitoring committee recommended dose modification for all patients receiving albIFN 1200 µg to 900 µg, impacting 38% of this treatment arm.

RESULTS—By intention-to-treat analysis, SVR rates were 84.8% (95% confidence interval, 80.4%–88.6%), 79.8% (95% confidence interval, 74.9%–84.1%), and 80.0% (95% confidence interval, 75.1%–84.3%) with Peg-IFNalfa-2a, and albIFN 900 and 1200 µg, respectively. The primary hypothesis of noninferiority of SVR was established for albIFN 900 µg ($P = .009$) and 1200 µg ($P = .006$). Independent positive predictors of SVR by multivariate regression analysis were pretreatment HCV-RNA level less than 400,000 IU/mL, age younger than 45 years, body mass index less than 30 kg/m², genotype 2, normal γ -glutamyl transpeptidase and increased alanine aminotransferase levels at baseline, fibrosis stage F0–F2, no steatosis, and Asian geographic region (Peg-IFNalfa-2a only). The 3 treatment groups showed similar rates of serious (7%–8%) and severe (13%–16%) adverse events, and discontinuations owing to adverse events (3.6%–5.5%).

CONCLUSION—Albinterferon alfa-2b 900 µg every 2 weeks provides an alternative efficacious treatment option in patients with chronic HCV genotype 2 or 3.

Keywords

ACHIEVE; albIFN; Pegylated Interferon-Alfa; Sustained Virologic Response

Chronic infection with hepatitis C virus (HCV) is a major cause of chronic liver disease worldwide. The global prevalence and distribution of HCV genotypes vary by geographic location among the estimated 170 million infected people.^{1,2} In North America and Western Europe, HCV genotypes 2 and 3 represent 20%–40% of chronic HCV infections, whereas reported prevalence rates are as high as 60% in Southeast Asia.^{3,4} The current standard of care for the treatment of chronic HCV genotype 2 or 3 is 24 weeks of pegylated interferon-alfa (Peg-IFNalfa) administered weekly in combination with fixed-dose oral ribavirin (800 mg/day), which results in sustained virologic response (SVR) rates of 70%–85%.^{5–8} Thus, although current treatment options are effective, new IFNs under development have positioned themselves to offer some combination of the following: (1) improved viral suppression, (2) more convenient dosing schedules, (3) optimized pharmacokinetics, and (4) reduced adverse events (AEs).⁹

Albinterferon alfa-2b (albIFN) is a single polypeptide that comprises human IFNalpha-2b genetically fused to human albumin.¹⁰ Human serum albumin is a natural carrier protein with a long half-life, and the genetic fusion of albumin to IFNalpha-2b extends the half-life of the recombinant polypeptide to approximately 200 hours while maintaining biological activity over a 2- to 4-week interval.^{11,12} The selection of the albIFN 900- and 1200- μ g doses and the biweekly injection schedule was based on the dose-dependent antiviral activity observed in patients with chronic HCV genotype 1.¹³ The present study, ACHIEVE-2/3, evaluated the efficacy and safety of albIFN 900 and 1200 μ g every 2 weeks compared with Peg-IFNalpha-2a 180 μ g/wk, all in combination with oral ribavirin for a 24-week treatment duration, in patients with chronic HCV genotype 2 or 3.

Materials and Methods

Study Oversight

The study sponsors (Human Genome Sciences, Inc, Rockville, MD, and Novartis Pharma AG, Basel, Switzerland) and academic principal investigators were jointly responsible for the study design, protocol, statistical analysis plan, and data analysis. A trial steering committee comprising study investigators provided oversight of the conduct of the program, and an independent data monitoring committee (DMC) was responsible for review of safety data during the study. The principal investigators had unrestricted access to the data, wrote this manuscript, and provided assurance for the accuracy of the reported analysis.

Patient Selection

Adult patients with chronic HCV genotype 2 or 3 who had not received IFNalpha therapy previously were invited to participate in the study. 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, co-infection with hepatitis B virus or human immunodeficiency virus, a significant coexisting medical condition, or alcohol or drug dependence. All patients were required to have a liver biopsy performed within 2 years of enrollment.

Study Design

This phase 3 study was conducted at 136 centers worldwide, including Asia (37 sites; 271 patients), Australia (16 sites; 72 patients), Europe (39 sites; 247 patients), North America (39 sites; 313 patients), and South America (5 sites; 29 patients), between February 2007 and October 2008 (ClinicalTrials.gov no. NCT00411385).

All patients provided written informed consent, and the institutional review boards of participating centers approved the protocol. A centralized randomization stratified by genotype (2 or 3) and baseline serum HCV-RNA concentration ($\geq 800,000$ IU/mL or $< 800,000$ IU/mL) assigned patients using an interactive voice-response system in blocks of 3 in a 1:1:1 ratio to 1 of 3 open-label treatment groups: Peg-IFNalpha-2a 180 μ g/wk (Pegasys; Hoffmann-La Roche, Inc, Nutley, NJ), albIFN 900 μ g every 2 weeks, or albIFN 1200 μ g every 2 weeks. Albinterferon alfa-2b was provided as a sterile, single-use, lyophilized product for reconstitution before subcutaneous injection, and Peg-IFNalpha-2a was supplied in sterile, single-use, graduated, and prefilled syringe. All patients also received oral ribavirin (Ribasphere; Three Rivers Pharmaceuticals, Warrendale, PA) 800 mg/day in 2 divided doses. Treatment duration was 24 weeks, with follow-up evaluation at 24 weeks after the end of treatment for SVR assessment. The study protocol specified stepwise (≥ 1 level) dose reductions of albIFN to 900, 700, and 500 μ g, and of Peg-IFNalpha-2a to 135, 90,

and 45 µg, to manage hematologic abnormalities and moderate-severe AEs. The use of hematopoietic growth factors was not permitted.

Efficacy Assessments

Serum HCV-RNA levels were measured by real-time polymerase chain reaction assay (COBAS Ampli-prep/COBAS TaqMan HCV Test, F. Hoffmann-La Roche Ltd; limit of detection, 15 IU/mL; lower limit of quantitation, 43 IU/mL) at weeks 2, 4, 6, 8, 12, 16, 20, and 24 during the treatment phase, and at weeks 28, 36, and 48 after treatment. The primary end point was SVR, defined as undetectable HCV-RNA levels (<15 IU/mL) at week 48 (24 weeks after treatment).

Safety Assessments

Safety was assessed by physical examination and laboratory assessments during the treatment phase through 12 or more weeks after completion of therapy to document resolution of any ongoing AEs. Dose reductions of one or both drugs were permitted to manage clinically significant AEs or laboratory abnormalities. The IFN dose could be withheld for up to 6 weeks before discontinuation of the patient from the study. The independent DMC reviewed data on an ongoing basis for both this and a companion phase 3 study in patients with chronic HCV genotype 1 (ClinicalTrials.gov no. NCT0040248).

In December 2007, after a median of 4 months on treatment, the DMC recommended assessment of pulmonary function in all patients enrolled in both phase 3 albIFN studies after 2 reports of interstitial lung disease in the albIFN 1200-µg every-2-weeks group of the ACHIEVE-1 study, which was conducted in parallel to ACHIEVE-2/3. Chest radiograph interpretation was provided by study sites, and additional blinded central assessment of all chest radiographs was performed. In January 2008, the DMC recommended modification of the study protocol because of a concern for increased pulmonary AEs in the albIFN 1200-µg arm. At the time that this dose reduction was implemented, only 118 of 310 patients (38.1%) in the albIFN 1200-µg treatment arm were still on treatment, and all had completed 12 or more weeks of therapy.

Liver Pathology and Insulin Resistance

Pretreatment percutaneous liver biopsies were evaluated for fibrosis staging using the METAVIR score and were graded for liver steatosis by a central blinded pathologist.^{14,15} All biopsies had been obtained within 2 years of study enrollment. Fasting serum samples were collected at day 0 for glucose and insulin levels to assess insulin resistance using homeostasis model assessment of insulin resistance.¹⁶

Statistical Methods

At least 306 patients per treatment group were targeted to be randomized and treated in this study. Assuming an SVR rate of 77.2% for each treatment group based on meta-analysis of historical data,^{5-6,17} this sample size provided 90% power to establish noninferiority of each albIFN dose level relative to Peg-IFNalpha-2a, with a noninferiority margin of 12% and an overall one-sided α significance value of .025 (adjusted for multiple doses).^{18,19} The choice of the 12% noninferiority margin was based on a combination of statistical reasoning and clinical judgment. The active control effect was estimated conservatively using the lower bound of the 95% confidence interval (CI) obtained from a meta-analysis of Peg-IFNalpha-2a registration trials; the 12% margin preserved more than 80% of this effect. In addition, this margin was discussed with the US Food and Drug Administration and other regulatory agencies, along with global clinical experts; there was universal acceptance of the margin and the efficacy it would confer. The primary analysis was performed in the intention-to-

treat population, including all randomized patients who received 1 or more doses of study agent, and was adjusted for HCV-RNA level and genotype stratification. There was no change to the planned analysis after the DMC modification to the albIFN 1200- μ g group. In addition, a per-protocol analysis included patients who received the treatment assigned via randomization, met major entry criteria, completed treatment with 80% or more adherence to both IFN and ribavirin components of therapy, and did not have missing SVR data. Safety analyses were performed on the as-treated population to address 1 patient randomized to Peg-IFNalpha-2a who received albIFN 900 μ g throughout.

In addition, presence of SVR was modeled via multivariate logistic regression using an automated backward selection approach as a function of treatment group; genotype; sex; weight 75 kg or greater; body mass index <25, 25–29, or ≥ 30 kg/m²; age (≥ 45 year); alanine aminotransferase level greater than 1.5 times the upper limit of normal; γ -glutamyl transpeptidase level less than or equal to the upper limit of normal; advanced fibrosis (F3–F4); Asian region versus the rest of the world; Hispanic/Latino ethnicity; baseline HCV-RNA level <400,000, 400,000–799,999, or $\geq 800,000$ IU/mL; insulin resistance (homeostasis model assessment of insulin resistance, >2); and steatosis. Ordinal 3-level variables (HCV-RNA level and body mass index) were modeled with indicator variables; the terms retained discriminated between cut-off levels, whereas those not retained resulted in collapsing of adjacent categories. In addition, all 2-way interactions of these factors with both albIFN treatment groups, as well as genotype, were included as potential predictors to allow these factors to have differential impact by either treatment group or genotype. All analyses were performed using SAS 9 (SAS Institute, Inc, Cary, NC) and R (version 1.9.1) statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Disposition and Demographics

In all, 1301 patients were screened to yield 933 randomized patients, of whom 932 received 1 or more doses of study agent (Figure 1). The most common reasons for screening failure were decompensated liver disease, and failing to meet minimal hematologic and biochemical criteria. Completion rates were similar across treatment groups and the rates of patients missing SVR data were low (2.3%–3.2%). Patient demographics and disease characteristics were similar among treatment groups (Table 1).

Efficacy

The primary efficacy hypothesis of noninferiority to Peg-IFNalpha-2a was established for both the albIFN 900- and 1200- μ g groups. In the Peg-IFNalpha-2a group, 84.8% (95% CI, 80.4%–88.6%) of patients achieved an SVR compared with 79.8% (95% CI, 74.9%–84.1%) in the albIFN 900- μ g group ($P = .009$ for noninferiority; adjusted difference, -4.8% ; 95% CI, -10.7% – 1.1%) and 80.0% (95% CI, 75.1%–84.3%) in the albIFN 1200- μ g group ($P = .006$ for noninferiority; adjusted difference, -4.5% ; 95% CI, -10.3% – 1.4% ; Figure 2 and Supplementary Table 1). Noninferiority of SVR rates also was established in the per-protocol population for albIFN 900 μ g ($P = .02$; adjusted difference, -3.8% ; 95% CI, -9.3% – 1.8%) and 1200 μ g ($P = .02$; adjusted difference, -5.9% ; 95% CI, -11.6% – 0.1%). The SVR rates were higher in patients with genotype 2 (90.2% with Peg-IFNalpha-2a, 81.0% with albIFN 900 μ g, and 81.7% with albIFN 1200 μ g) than with genotype 3 (80.2%, 78.8%, and 78.6%, respectively; Figure 2 and Supplementary Table 2).

Multivariate logistic regression modeling was performed to investigate predefined covariate effects (Figure 3). Baseline viral load less than 400,000 IU/mL, age younger than 45 years, and body mass index less than 30 kg/m² were strongly associated ($P \leq .001$) with a higher

likelihood of an SVR across all treatment groups. In addition, genotype 2, baseline γ -glutamyl transpeptidase level less than the upper limit of normal, baseline alanine aminotransferase greater than 1.5 times the upper limit of normal, no steatosis at baseline, and fibrosis F0–F2 were associated with achieving an SVR. Asian region, but only for the Peg-IFNalpha-2a group ($P = .01$), also was associated with a higher SVR rate. Finally, weight of 75 kg or greater was associated with a lower likelihood of an SVR ($P = .02$), but only in the albIFN 1200- μ g group.

The observed difference in SVR rates between the Peg-IFNalpha-2a and albIFN treatment groups appears to be owing to an SVR difference between treatment groups in Asian countries, which persisted when controlling for baseline factors in the multivariate analysis. This was explored further in a post hoc analysis (Table 2 and Supplementary Table 3). A higher SVR rate in the Peg-IFNalpha-2a group was observed in the Asian region (95.5%) compared with other regions (80.5%), whereas the albIFN groups showed SVR rates in the Asian region (79.8%–81.8%) that were consistent with other regions (79.3%–79.8%). Further, a difference in response between albIFN and Peg-IFNalpha-2a in Asia was observed by treatment week 4 before any significant IFN or ribavirin dose adjustments could occur. Rates of undetectable HCV-RNA levels at week 4 in Asia were 76%, 59%, and 65% in the Peg-IFNalpha-2a, and albIFN 900- μ g, and 1200- μ g groups, respectively. The high treatment completion rates for Peg-IFNalpha-2a (100%) coupled with better week-4 response rates and differences in ribavirin adherence (discussed later) may have contributed to the observed difference in SVR rates in Asia.

Safety and Tolerability

The overall safety profile (AEs and laboratory values) was comparable among the 3 treatment groups. In particular, severe (grade 3 or 4) and/or serious AE rates were similar across treatment groups (Table 3). The rates of treatment discontinuation because of AEs were low and comparable between treatment groups: 3.6% (11 of 309) with Peg-IFNalpha-2a, 4.8% (15 of 313) with albIFN 900 μ g, and 5.5% (17 of 310) with albIFN 1200 μ g. There were 4 deaths reported in the study (1 with Peg-IFNalpha-2a as a result of morphine overdose, 1 with albIFN 900 μ g as a result of sepsis, and 2 with albIFN 1200 μ g as a result of sepsis and narcotic overdose, respectively).

The most frequent AEs were common side effects of IFN therapy and the majority of these occurred at similar rates across treatment groups (Table 3). The AEs that occurred at higher rates in the albIFN groups compared with the Peg-IFNalpha-2a group included alopecia (43%–44% vs 25%), cough (38%–41% vs 29%), and weight loss (25%–28% vs 15%), whereas anxiety was higher with Peg-IFNalpha-2a (12% vs 7%). Patients in all groups who experienced cough (mostly mild) reported an onset of symptoms between treatment weeks 4 and 12, with resolution of cough occurring a median of 4 weeks after treatment (Supplementary Figure 1 and Supplementary Table 4). Alopecia (ie, hair thinning or effluvium) was mostly mild in severity and was first reported around treatment week 8, with resolution after completion of treatment. The incidence of alopecia was higher in women for all 3 treatment groups. Although the rates were significantly higher in the albIFN groups, alopecia resolved after treatment completion in a similar fashion across all treatment groups with respect to both actual resolution and timing of resolution. There were no differences in the rates of severe or serious respiratory AEs or respiratory infections between the 3 treatment groups (Supplementary Tables 5 and 6). Consistent with these findings, the rates of chest radiograph interstitial findings assessed via blinded central review were low and comparable among treatment groups. Rates of neutrophil and platelet reductions were similar in the Peg-IFNalpha-2a and albIFN 900- μ g groups and higher in the albIFN 1200- μ g group. Reduced neutrophil or lymphocyte counts were not associated with severe and/or serious infections. Reductions in hemoglobin levels were highest in the albIFN 1200- μ g

group, corresponding to a trend toward more ribavirin dose reductions (Table 3). Rates of anemia were higher in lower-weight patients in all 3 treatment groups; analysis controlling for sex indicated that this was driven primarily by sex and not actual body weight. Across all treatment groups, hematologic reductions stabilized by treatment week 8, with recovery to pretreatment levels after completion of treatment.

The safety profiles of Peg-IFNalpha-2a and albIFN in patients in Asia also were explored in a post hoc analysis (Table 4). Of note, treatment discontinuation rates were 0% in the Peg-IFNalpha-2a group compared with 3.2%–3.4% in the albIFN groups, whereas the rates outside Asia ranged from 5.0% to 6.3% for all treatment groups. Rates of neutropenia were no different across groups, but there was a trend toward more frequent hemoglobin reductions with albIFN than with Peg-IFNalpha-2a, resulting in more ribavirin dose reductions with albIFN.

Discussion

Albumin-fusion technology represents a novel and flexible alternative platform for the production of proteins with extended circulatory half-lives to optimize drug exposure.¹⁰ Albinterferon alpha-2b represents the first large-scale clinical validation of the albumin-fusion technology platform to provide sustained biological activity, with the enhanced convenience of a reduced dosing schedule of administration every 2 weeks. The present phase 3 study met the primary hypothesis of noninferior efficacy of albIFN compared with Peg-IFNalpha-2a. The SVR rates in the intention-to-treat population were 80%–85% and compared favorably with other randomized clinical trials evaluating 24-week Peg-IFNalpha/ribavirin treatment in patients with chronic HCV genotype 2 or 3.^{6,8} The midtrial dose modification likely did not impact assessment of efficacy because all patients had completed 12 weeks of treatment at the time of the dose reduction in the albIFN 1200-μg study arm, and the virologic-response profiles were similar in the albIFN 900-μg and 1200-μg arms. The similar SVR rates indicate that albIFN exposure at 900 μg every 2 weeks is sufficient in a chronic HCV genotype 2 or 3 population. Furthermore, this large global study showed that predictors of SVR for albIFN were similar to those for Peg-IFNalpha-2a. In particular, it confirms the importance of steatosis as an independent predictor of poor virologic response in addition to previously described factors such as advanced liver fibrosis, high γ-glutamyl transpeptidase level, genotype 3, and high viral load.⁸

Given the high positive predictive value of rapid virologic response by treatment week 4 for achieving SVR, several recent studies have explored shortening the duration of treatment based on the early kinetics of virologic response.^{20,21} In the present study, earlier time to HCV-RNA negativity was highly predictive of SVR for all treatment arms and supports future study of viral kinetics–based treatment regimens with albIFN in patients with chronic HCV genotype 2 or 3 (Supplementary Tables 7 and 8). Although SVR rates for albIFN were consistent across all geographic regions, the rate was higher in the Peg-IFNalpha-2a group among patients from Asian countries. The higher SVR rate in these patients likely was owing to a greater proportion achieving rapid virologic response and 100% completing treatment. The higher rapid virologic response rate in these patients remains unexplained because there were no differences in Peg-IFNalpha-2a or albIFN drug plasma levels over the first 4 treatment weeks or in baseline characteristics evaluated among the treatment groups. Further, lower ribavirin exposure in the albIFN groups as a result of more hemoglobin reductions compared with the Peg-IFNalpha-2a group may have contributed to the overall difference in SVR rates (as shown by the higher relapse rates in the albIFN arms in the Asian population). Although high SVR rates have been reported previously among Asians with chronic HCV genotype 2 or 3 receiving weight-based ribavirin for 24 weeks,^{22,23} the constraints of a small sample size and post hoc analysis indicate the need for further studies

to assess the reproducibility of these findings. Recent studies have shown associations between pretreatment hepatic gene expression profiles and a polymorphism in the *interleukin-28B* gene with virologic response in patients with chronic HCV genotype 1.^{24,25} Of note, the highest frequency of the favorable genetic polymorphism (C-allele) is found in East Asians and strongly correlates with SVR.^{24,26} In this study, DNA samples were not collected from patients and thus genetic factors were not assessed. Future studies to evaluate hepatic gene expression and host genetic polymorphisms affecting IFN-stimulated responses in Asian populations may provide further insights into the observed discordant virologic response based on ethnicity in the present study.

The overall safety of albIFN was comparable with that of Peg-IFNalpha-2a in terms of the types of AEs and the frequency of severe or serious AEs over the 24-week treatment duration. Neutrophil and platelet reductions in the albIFN 900-μg group were comparable with those in the Peg-IFNalpha-2a group. Respiratory AEs warrant special consideration and discussion, given that they were the reason for the midtrial change to reduce the dose of albIFN in the 1200-μg group. Respiratory AEs are observed commonly during IFNalpha-based chronic HCV therapy and may include rare, although serious, events of interstitial lung disease, as noted in the product labeling for the Peg-IFNalfas.^{27–30} Although cough was observed more commonly with albIFN, these AEs were mostly mild and resolved after completion of therapy. Interstitial findings on chest radiographs that were obtained as part of the DMC-recommended assessment revealed no differences across treatment groups. Importantly, there was no occurrence of progressive interstitial lung disease or increased risk of serious pulmonary AEs observed in the albIFN groups in this study.

In summary, this phase 3 study showed that the efficacy and safety of albIFN 900 μg every 2 weeks was comparable with Peg-IFNalpha-2a 180 μg/wk in a global cohort of patients with chronic HCV genotype 2 or 3. The data suggest that albIFN could provide the option of less frequent IFN dosing in patients with chronic HCV genotype 2 or 3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The statistical analysis of the entire data sets pertaining to efficacy (specifically primary and major secondary efficacy end points) and safety (specifically serious adverse events as defined in federal guidelines) have been confirmed independently by a biostatistician who is not employed by the corporate entity. The corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and analysis.

Funding This study was supported by Human Genome Sciences.

Abbreviations used in this paper

AE	adverse event
albIFN	albinterferon alfa-2b
CI	confidence interval
DMC	data monitoring committee
F	fibrosis score
Peg-IFNalpha	pegylated interferon-alfa
SVR	sustained virologic response

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Figure 1.

Disposition of patients. ¹Randomized to Peg-IFNα-2a 180-µg/wk group. ²As treated; 1 patient was randomized to Peg-IFNα-2a 180-µg, but received albIFN 900 µg every 2 weeks. EVR12, early virologic response at week 12.

Figure 2.
SVR rates (overall and in genotype 2 or 3).

Figure 3.

Predictors of SVR by multivariate regression model. Model-based adjusted odds ratios and associated 95% CIs for factors provided along the y-axis. *Plotting symbol* represents odds ratio; *horizontal line* spans coverage of CI. *Vertical reference line* at odds ratio of 1 indicates no difference. Note: Asian region subgroup shown at top of figure is post hoc analysis. ALT, alanine aminotransferase; BMI, body mass index; F, fibrosis score; GGT, γ -glutamyl transpeptidase; ULN, upper limit of normal; wt, weight.

Table 1

Baseline Characteristics

Characteristic	Peg-IFNalpha-2a 180 µg/wk (n = 310)	albIFN 900 µ every 2 weeks (n = 312)	albIFN 1200 µ every 2 weeks (n = 310)
Male sex, n (%)	175 (56.5)	186 (59.6)	184 (59.4)
Mean age ± SD, y	44.1 ± 10.6	45.3 ± 11.7	44.1 ± 11.5
≥45 y, n (%)	155 (50.0)	169 (54.2)	163 (52.6)
Mean BMI ± SD, kg/m ²	25.7 ± 4.7	26.2 ± 4.5	26.2 ± 5.5
<25 kg, n (%)	135 (43.5)	117 (37.5)	136 (43.9)
≥25 to <30 kg, n (%)	126 (40.6)	127 (40.7)	109 (35.2)
≥30 kg, n (%)	49 (15.8)	68 (21.8)	65 (21.0)
Mean weight ± SD, kg	72.9 ± 15.9	74.9 ± 17.4	75.4 ± 19.1
≥75 kg, n (%)	120 (38.7)	143 (45.8)	137 (44.2)
HCV genotype, n (%)			
2	143 (46.1)	142 (45.5)	142 (45.8)
3	167 (53.9)	170 (54.5)	168 (54.2)
Race/ethnic group, n (%)			
White	196 (63.2)	192 (61.5)	200 (64.5)
Black/African heritage	4 (1.3)	8 (2.6)	5 (1.6)
Asian	99 (31.9)	104 (33.3)	100 (32.3)
Multiracial	1 (0.3)	-	1 (0.3)
Other	10 (3.2)	8 (2.6)	4 (1.3)
Mean serum HCV-RNA level ± SD, log ₁₀ IU/mL	5.9 ± 0.9	5.9 ± 0.9	6.0 ± 0.9
<400,000 IU/mL, n (%)	93 (30.0)	97 (31.1)	93 (30.0)
≥400,000 to <800,000 IU/mL, n (%)	35 (11.3)	27 (8.7)	26 (8.4)
≥800,000 IU/mL, n (%)	182 (58.7)	188 (60.3)	191 (61.6)
Mean ALT level ± SD, IU/L	90.4 ± 67.9	95.9 ± 83.6	101.2 ± 84.8
>1.5× ULN, n (%)	156 (50.3)	152 (48.7)	164 (52.9)
GGT level ≤ULN, n (%)	234 (75.5)	236 (75.6)	221 (71.3)
HOMA-IR score >2	129/257 (50.2)	129/253 (51.0)	129/254 (50.8)
Any steatosis, n (%)	107 (34.5)	119 (38.1)	121 (39.0)
F3-F4, n (%)	27/304 (8.9)	41/310 (13.2)	36/308 (11.7)

ALT, alanine aminotransferase; BMI, body mass index; F, fibrosis score; GGT, γ-glutamyl transpeptidase; HOMA-IR, homeostasis assessment of insulin resistance; SD, standard deviation; ULN, upper limit of normal.

Table 2

Virologic Response Rates in Patients Enrolled in Sites in Asia Compared With the Rest of the World

Response	Peg-IFNalpha-2a 180 µg/wk, n/N (%)	albIFN 900 µg every 2 weeks, n/N (%)	albIFN 1200 µg every 2 weeks, n/N (%)
RVR: week-4 HCV-RNA level <LOD			
Overall	182/310 (58.7)	150/312 (48.1)	159/310 (51.3)
Asia	68/89 (76.4)	55/94 (58.5)	57/88 (64.8)
Rest of the world	114/221 (51.6)	95/218 (43.6)	102/222 (45.9)
ETR: week-24 HCV-RNA level <LOD			
Overall	296/310 (95.5)	293/312 (93.9)	293/310 (94.5)
Asia	89/89 (100.0)	85/94 (90.4)	84/88 (95.5)
Rest of the world	207/221 (93.7)	208/218 (95.4)	209/222 (94.1)
Relapse			
Overall	33/296 (11.1)	44/293 (15.0)	45/293 (15.4)
Asia	4/89 (4.5)	10/85 (11.8)	12/84 (14.3)
Rest of the world	29/207 (14.0)	34/208 (16.3)	33/209 (15.8)
SVR			
Overall	263/310 (84.8)	249/312 (79.8)	248/310 (80.0)
Asia	85/89 (95.5)	75/94 (79.8)	72/88 (81.8)
Rest of the world	178/221 (80.5)	174/218 (79.8)	176/222 (79.3)

ETR, end-of-treatment response; LOD, limit of detection; RVR, rapid virologic response.

Table 3

Discontinuations, Dose Modifications, Adverse Events, and Laboratory Reductions

	Peg-IFNalpha-2a 180 µg/ wk (n = 309), n (%)	albIFN 900 µ every 2 weeks (n = 313), n (%)	albIFN 1200 µ every 2 weeks (n = 310), n (%)
Serious AE	23 (7.4)	24 (7.7)	22 (7.1)
Severe AE	48 (15.5)	42 (13.4)	43 (13.9)
Death	1 (0.3)	1 (0.3)	2 (0.6)
Discontinuation owing to AE	11 (3.6)	15 (4.8)	17 (5.5)
IFN dose reduction owing to AE	22 (7.1)	21 (6.7)	36 (11.6)
IFN dose reduction owing to laboratory abnormality	37 (12.0)	35 (11.2)	39 (12.6)
Ribavirin dose reduction owing to laboratory abnormality	40 (12.9)	56 (17.9)	60 (19.4)
Medical Dictionary for Regulatory Activities preferred term (<10% frequency in any treatment group)			
Headache	138 (44.7)	140 (44.7)	137 (44.2)
Fatigue	125 (40.5)	127 (40.6)	138 (44.5)
Pyrexia	113 (36.6)	120 (38.3)	136 (43.9)
Alopecia	77 (24.9)	137 (43.8)	133 (42.9)
Cough	88 (28.5)	129 (41.2)	118 (38.1)
Insomnia	107 (34.6)	108 (34.5)	105 (33.9)
Myalgia	90 (29.1)	100 (31.9)	127 (41.0)
Nausea	81 (26.2)	76 (24.3)	84 (27.1)
Pruritus	74 (23.9)	89 (28.4)	77 (24.8)
Arthralgia	73 (23.6)	79 (25.2)	68 (21.9)
Weight decreased	47 (15.2)	78 (24.9)	86 (27.7)
Diarrhea	58 (18.8)	56 (17.9)	60 (19.4)
Rash	56 (18.1)	60 (19.2)	58 (18.7)
Anorexia	47 (15.2)	59 (18.8)	59 (19.0)
Asthenia	49 (15.9)	52 (16.6)	46 (14.8)
Dizziness	44 (14.2)	44 (14.1)	59 (19.0)
Influenza-like illness	46 (14.9)	50 (16.0)	47 (15.2)
Chills	49 (15.9)	46 (14.7)	47 (15.2)
Dry skin	46 (14.9)	48 (15.3)	45 (14.5)
Mood altered	44 (14.2)	46 (14.7)	47 (15.2)
Depression	43 (13.9)	50 (16.0)	42 (13.5)
Dyspnea	43 (13.9)	30 (9.6)	56 (18.1)
Vomiting	34 (11.0)	35 (11.2)	46 (14.8)
Dry mouth	28 (9.1)	34 (10.9)	46 (14.8)
Decreased appetite	24 (7.8)	24 (7.7)	40 (12.9)
Injection-site erythema	36 (11.7)	27 (8.6)	22 (7.1)
Back pain	33 (10.7)	20 (6.4)	29 (9.4)
Anxiety	38 (12.3)	23 (7.3)	21 (6.8)
Absolute neutrophil count			

	Peg-IFNalpha-2a 180 µg/ wk (n = 309), n (%)	albIFN 900 µ every 2 weeks (n = 313), n (%)	albIFN 1200 µ every 2 weeks (n = 310), n (%)
<750/mm ³	62 (20.1)	57 (18.2)	87 (28.1)
<500/mm ³	10 (3.2)	17 (5.4)	18 (5.8)
<350/mm ³	4 (1.3)	6 (1.9)	4 (1.3)
Platelets			
<50,000/mm ³	12 (3.9)	12 (3.8)	18 (5.8)
<25,000/mm ³	2 (0.6)	1 (0.3)	1 (0.3)
Hemoglobin level			
<10 g/dL	53 (17.2)	71 (22.7)	74 (23.9)
<8.5 g/dL	6 (1.9)	11 (3.5)	14 (4.5)
On-treatment chest radiograph	219 (70.9)	224 (71.6)	211 (68.1)
Interstitial finding ^a	11/219 (5.0)	14/224 (6.3)	11/211 (5.2)

^aExactly 1 lower lobe or both lungs.

Table 4

Safety in Patients Enrolled in Sites in Asia Compared With the Rest of the World

Adverse events	Peg-IFNalpha-2a 180 µg/ wk, n/N (%)	AlbIFN 900 µg every 2 weeks, n/N (%)	AlbIFN 1200 µg every 2 weeks n/N (%)
Serious AE			
Asia	6/88 (6.8)	10/95 (10.5)	6/88 (6.8)
Rest of the world	17/221 (7.7)	14/218 (6.4)	16/222 (7.2)
Severe AE			
Asia	5/88 (5.7)	9/95 (9.5)	14/88 (15.9)
Rest of the world	43/221 (19.5)	33/218 (15.1)	29/222 (13.1)
Discontinuation owing to AE			
Asia	0/88 (0.0)	3/95 (3.2)	3/88 (3.4)
Rest of the world	11/221 (5.0)	12/218 (5.5)	14/222 (6.3)
Absolute neutrophil count, <750/mm ³			
Asia	29/88 (33.0)	28/95 (29.5)	32/88 (36.4)
Rest of the world	33/221 (14.9)	29/218 (13.3)	55/222 (24.8)
Platelets, <50,000/mm ³			
Asia	3/88 (3.4)	5/95 (5.3)	5/88 (5.7)
Rest of the world	9/221 (4.1)	7/218 (3.2)	13/222 (5.9)
Hemoglobin level, <10 g/dL			
Asia	25/88 (28.4)	34/95 (35.8)	39/88 (44.3)
Rest of the world	29/221 (13.1)	38/218 (17.4)	35/222 (15.8)
Ribavirin dose reduction owing to laboratory abnormality			
Asia	20/88 (22.7)	27/95 (28.4)	35/88 (39.8)
Rest of the world	20/221 (9.0)	29/218 (13.3)	25/222 (11.3)