January 2, 2001

MEMORANDUM

FROM Louis Marzella M.D., Ph.D, Medical Reviewer.

THROUGH William Schwieterman M.D., Chief, Immunology and Infectious Diseases Branch.

TO Karen Weiss M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, CBER.

TOPIC Clinical Review
Biologic License Application 99-14888
PEG-Intron™ SCH54031 (PEG_{12000}-Interferon alfa-2b)

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INTRODUCTION

Product

Drug Substance:

PEG-Intron™, peg-interferon alfa-2b, is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy polyethylene glycol product. The biological activity of peg-interferon alfa-2b is derived from its interferon alfa-2b moiety.

Interferon alfa-2b has been classified as an alpha interferon and is a water-soluble protein with a molecular weight of approximately 19,000 daltons produced by recombinant DNA techniques. Interferon alfa-2b is obtained from the bacterial fermentation of a strain of *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alfa-2b gene from human leukocytes. The average molecular weight of the PEG-Intron molecule is approximately 31,000 daltons.

Drug Product:

PEG-Intron is a white to off-white lyophilized powder supplied in 2-mL vials for subcutaneous injection. Each vial contains either 74 μg, 118.4 μg, 177.6 μg or 222 μg of PEG-Intron, and 1.11 mg dibasic sodium phosphate, 1.11 mg monobasic sodium phosphate, 59.2 mg sucrose and 0.074 mg polysorbate 80. Before administration, PEG-Intron is reconstituted with 0.7 ml provided diluent (Sterile Water for Injection, USP). Following reconstitution with 0.7 ml of the supplied diluent (Sterile Water for Injection, USP), each vial contains PEG-Intron at strengths of either 100μg, 160μg, 240μg or 300μg per ml of reconstituted product.

Pharmacokinetics

Peg-interferon alfa is rapidly absorbed following a single dose administered subcutaneously (mean absorption half-life [t ½ k_a] = 4.6 hours). Maximal serum concentrations (C_{max}) occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose. The C_{max} and AUC measurements of peg-interferon alfa increase in a dose-related manner. Upon multiple dosing, there is an increase in bioavailability, with an accumulation factor of approximately four-fold for AUC(tf) after 48 weeks of dosing. The mean peg-interferon alfa elimination half-life is approximately 40 hours. Apparent clearance is estimated to be approximately 22.0 ml/hr·kg. Renal elimination accounts for approximately 30% of the clearance.

Single dose PEG-Intron pharmacokinetics following a subcutaneous 1.0 μg/kg dose suggest the clearance of PEG-Intron is reduced in patients with impaired renal function (creatinine clearance < 50 ml/minute). Pharmacokinetic evaluations for pediatric subjects have not been performed. There were no significant pharmacokinetic differences between male and female patients with chronic hepatitis C.

Chronic Viral Hepatitis C

Hepatitis C virus (HCV) is transmitted primarily through direct percutaneous exposure to blood. HCV infects an estimated 3 million people in the United States. A high proportion of infected patients develops chronic liver disease. Chronic hepatitis C results in an estimated 8,000 to 10,000 deaths each year. After 2-3 decades of HCV infection, 20% of patients may develop cirrhosis and about 1-2% of subjects develop hepatocellular carcinoma.

OVERVIEW OF CLINICAL STUDIES

The clinical studies included: one single-dose and one multiple-dose, dose-escalation phase 1 studies, one 20-week treatment protocol, and one dose-ranging phase 3 study. The clinical studies of peg-interferon are summarized in Table 1 and are reviewed below.

Table 1. Clinical Studies of Peg-interferon Alfa-2b

STUDY NUMBER	STUDY DESIGN	DOSES	N
Phase 1 Studies			
I95-010	Randomized, double-blind, active-control, single-dose, dose-escalation in normal subjects.	Peg-interferon (0.035, 0.07, 0.14, 0.35, 0.5 or 0.7μg/kg) or interferon (3 MIU or 10 MIU) SC	60
I95-060	Randomized, open-label, active control, multiple-dose, dose-escalation study in subjects with HCV. Treatment for 4 weeks.	Peg-interferon (0.035, 0.1, 0.25, 0.5, 1.0, 1.5 or 2.0 μg/kg) QW SC, or 0.5 μg/kg BIW SC. Interferon (3 MIU TIW SC)	64
I95-140	Extension of protocol I95-060 with 20-week treatment period and follow-up at 4 weeks post-treatment.	Same as for protocol I95-060	64
Phase 3 Study			
C/I97-010	Randomized, active control, dose-ranging study with 48-wks treatment and 24-wks follow-up.	Peg-interferon 0.5, 1.0 or 1.5 μg/kg QW SC or interferon alfa 3MIU TIW SC	1219

N is the number of patients enrolled in each study.

PHASE 1 STUDIES

Protocol I95-010-01.
Study Title. "Rising Single-dose Safety and Tolerability of PEG 2000 Interferon alfa-2b in Healthy Volunteers"

Study Objective. The objective of this rising single-dose study was to determine the safety, tolerability and pharmacokinetics of a single dose of peginterferon alfa-2b.

Study Protocol. This was a single-center (European), randomized (4:1), open-label, active-controlled (interferon alfa-2b $3x10^6$ or $10x10^6$ IU at 0, 48, and 96 hours) single-dose, dose-escalation study of peg-interferon (0.07, 0.14, 0.35, 0.7, 1.4, 3.5 μg/kg) in 60 normal subjects divided in six dose groups. Based on review of the safety data, escalation was stopped after dose group 4. Two new dose groups 0.035 and 0.5 μg/kg were studied.

Study Monitoring:
Physical examinations were performed at screening and at discharge from the study. Vital signs were obtained at specified times before and following dosing. Complete blood count and differential white blood cell counts were measured at screening, and at 0, 24, 48, 72, 96, 120, 144 and 168 hr post-treatment. Clinical chemistries and TSH were measured at screening, day -1 and 72 and 168 hours post-dose. Urinalysis was done at screening, day -1 and at 168 hours post-dose.

An ECG was obtained at screening, pre-treatment and 168 hr post-treatment. Serum interferon alfa-2b concentrations, neutralizing antibodies, serum neopterin and 2'5' oligo-adenylate synthetase were measured. Occurrence of adverse events were captured. Data were summarized using descriptive statistics.

Study Results:
Thirty one men and 29 women between 18 and 34 years and weighing between 50 and 90 participated in the study. Forty-eight subjects received peg-interferon alfa by subcutaneous administration and 12 subjects received interferon alfa.

There were no deaths or other serious adverse events. Four subjects developed grade 3 neutropenia after dosing with peg-interferon; one each after 0.35 and 0.5 μg/kg and two subjects after of 0.7 μg/kg. Reversible myelosuppression was considered dose limiting toxicity. One subject receiving interferon alfa developed grade 3 neutropenia. The most frequent adverse events reported after administration of peg-interferon were an influenza-like syndrome (46%), injection site reaction (58%), headache (46%), and fatigue/malaise (23%). All interferon alfa doses were associated with moderate decreases in platelet counts. Serum neopterin and 2'5'-OAS concentrations increased from baseline. Chemistries,

urinalyses and ECG showed no clinically significant changes. No subject developed neutralizing antibodies to interferon.

Compared with interferon alfa, peg-interferon alfa had a prolonged phase of maximal concentration half-life, approximately 7-fold greater. Apparent clearance estimates were approximately 10-fold lower for peg-interferon alfa than for interferon alfa.

Conclusions:
The safety profile of peg-interferon in this study was consistent with that of alpha interferons. The PK profile of peg-interferon alfa demonstrated a prolonged serum concentration-time profile compared with interferon alfa, and showed delayed clearance consistent with the effects of pegylation.

Protocol I95-060
Study Title. "SCH 54031: Rising, Multiple-Dose, Multicenter, Open-Label, Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Study of PEG 12000 Interferon alfa-2b in Patients with Chronic Hepatitis C".

Study Objectives. Assess safety and tolerability, pharmacokinetics and pharmacodynamics of multiple doses of peg-interferon alfa-2b.

Study Design. Randomized (3:1), single-center, open label, active-controlled (interferon 3 MIU TIW SC), multiple-dose, dose-escalation study of peg-interferon (0.035, 0.1, 0.25, 0.5, 1.0, 1.5 or 2.0 μg/kg QW SC), or 0.5 μg/kg BIW SC in 64 patients with chronic compensated hepatitis C. Subjects were naive to interferon treatment and were treated for four weeks.

Inclusion Criteria:
The following were the main inclusion criteria. Men or women age 18-68. Serum aminotransferase elevation within six months. Anti-HCV positive by supplemental assay (Ortho or Abbott) or HCV-RNA positive by immunoassay or PCR. Liver biopsy (within one year of enrollment) compatible with chronic hepatitis with no evidence of cirrhosis. No evidence of chronic hepatitis B or HIV infection. Acceptable baseline clinical laboratory values including: normal hemoglobin, platelets $\geq$100,000/mm ^{3}, normal WBC and granulocyte count. Serum bilirubin, albumin, creatinine, TSH normal.

Exclusion Criteria:
The following were the main exclusion criteria. Previous IFN treatment for hepatitis C. Alcoholic liver disease within one year of enrollment. Presence of concomitant liver disease including hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, drug-related liver disease, obesity-induced liver disease, autoimmune hepatitis. Parenteral antiviral or immunomodulatory therapy within the previous six months. Presence or history of significant medical illnesses.

Study Monitoring:

Safety was assessed by capturing adverse events, laboratory safety tests, physical examination, vital signs, injection site evaluations, ocular exams and ECG. PK/PD of PEG 12000 -interferon was assessed by measuring interferon alfa, 2',5', OAS, neopterin, and HCV-RNA titers. Data were summarized using means and standard deviations for C_{max}, T_{max}, AUCs.

Study Conduct:
The study was carried out in France. All study drugs were administered by study personnel. Two patients had their treatment allocation reversed. Laboratory abnormalities at baseline did not disqualify patients if the abnormalities were not judged to be significant. Patients who were $\pm$ 15 % outside normal body weight range and patients who tested positive for *Cannabis* were allowed to enter the study. Sixty-four adult, Caucasian men (N=42) and women (N=22) with chronic hepatitis C between the ages of 23 and 65 years and weighing between 45 and 95 kg were enrolled and completed the study.

Study Results:
No deaths or serious adverse events were reported in this study. The most frequently reported adverse events after administration of peg-interferon were asthenia (48%), headache (52%), and myalgia (23%). Peg-interferon produced elevation in body temperature, elevations in serum levels of effector proteins, and decreases in platelet, white cell and neutrophil counts. These changes were dose related for peg-interferon and at doses of 1.0-2.0 µg/kg once weekly were similar or slightly greater in magnitude compared to changes induced by interferon alfa.

Clearance estimates for peg-interferon were approximately 10-fold lower than these of interferon alfa, and half-life estimates were approximately 6-fold greater. The absorption and volume of distribution of both drugs were similar.

HCV-RNA titers at the end of treatment (week 4) were compared to titers at baseline. Decreases in titers of two orders of magnitude or more were interpreted as evidence of antiviral activity. Peg-interferon was active at doses $\geq$ 0.25 µg/kg. About 50% of patients receiving peg-interferon at doses between 0.5 and 2.0 µg/kg had lower viral titers ($\geq$2 log) compared to baseline.

Conclusions:
The reported frequency of adverse events for peg-interferon alfa-2b and interferon alfa-2b were similar. Pegylated interferon alfa-2b has reduced clearance relative to non-pegylated interferon permitting reduced dosing frequency at doses that appear to be pharmacologically active.

Protocol I95-140
Study Title. "Twenty-Week Treatment Continuation Protocol for Subjects with Chronic Hepatitis C Who Have Completed the Polyethylene Glycol-Interferon Alfa-2b (PEG-Intron, SCH 54031) Multiple Rising Dose Study" (Protocols I95-060 and I95-140).

Study Protocol:

The protocol was the same as study protocol I95-060. Patients were required to have completed all study requirements for I95-060and had to have no signs of intolerance to peg-interferon or interferon. Patients continued with open-label, previous treatment allocation and received 20 additional weeks of treatment (for a total of 24 weeks) and 4 weeks of post-treatment follow-up.

Study Outcomes:
Safety was assessed by review of adverse events and laboratory tests. Serum samples for pharmacokinetic analysis were collected for measurement and analysis in a separate study. ALT and HCV-RNA levels were summarized during treatment and at the end of follow-up. Virologic response was defined as undetectable serum HCV-RNA (<100 copies/ml of serum) at any time during treatment or follow-up. The study was not designed to statistically analyze the activity of peg-interferon. No inferential analyses were done.

Study Conduct:
All 64 subjects who were enrolled in I95-060 advanced to I95-140. Fifty-four subjects completed I95-140. The reasons for discontinuation were as follows. One subject (0.035 μg/kg peg-interferon) was lost to follow-up, four (0.1 μg/kg) and three (0.25 μg/kg peg-interferon) subjects were treatment failures, one subject (0.25 μg/kg peg-interferon) did not wish to continue, and one subject (interferon alfa-2b) was jailed for aggressive behavior.

Safety Results:
There were no deaths or life-threatening adverse events. There were two severe adverse events in the peg-interferon groups (diarrhea, and premenstrual tension syndrome). Laboratory abnormalities were generally of grade 2 or lower. The most frequently reported adverse event with the higher doses of peg-interferon (0.5-2.0 μg/kg QW) and with interferon were flu-like symptoms (asthenia, fever, headache).The type and frequency of adverse events for peg-interferon and interferon appeared to be similar.

Peg-interferon (0.1 μg/kg QW) dose was reduced in one subject because of weight loss. In the interferon alfa group dosing was interrupted in one subject because of lowered platelet count; dosing was discontinued in one subject because of aggressive behavior.

Activity Results:
The study protocol did not include a definition of activity endpoints. For the purpose of estimating antiviral activity the reviewer used the following post-hoc definition. Patients were considered to have responded to treatment if they were HCV-RNA positive at baseline and were HCV-RNA negative at the end of treatment (24 weeks) and at follow-up (4 weeks post-treatment). Patients with missing data (at baseline, end-of treatment, or post-treatment) were considered treatment failures for the purpose of this assessment.

In the three lower peg-interferon dose groups (≤0.25 μg/kg) one patient (1/18, 5%) responded to treatment. In the five higher peg-interferon dose groups (0.5-2.0 μg/kg QW and 0.5 μg/kg BIW) eight patients (8/30, 27%) responded to treatment. In each of the five highest dose groups, 1-2 patients out of six was a responder; therefore no dose-response trends were observed. In the interferon-treated group 2/16 patients (12%) responded to treatment.

Conclusions:
Peg-interferon alfa-2b administered for 24 weeks to subjects with chronic hepatitis C had an adverse event profile similar to that observed with interferon alfa-2b. Peg-interferon alfa-2b at doses ≥ 0.5 mg/kg showed antiviral activity similar to or numerically higher than that of interferon alfa-2b.

PHARMACOKINETIC STUDIES

The following three studies (Protocol C97-040, Protocol C97-058-01, Protocol I97-078) were reviewed primarily with regard to safety findings.

Protocol C97-040
Study Title. "SCH 54031: Single Dose Pharmacokinetics of PEG-Interferon Alfa-2b in Subjects with Various Degrees of Chronic Renal Insufficiency."

Study Objective. Determine the effect of renal dysfunction and hemodialysis on the pharmacokinetics of peg-interferon alfa-2b.

Study Design. Open-label, single-dose, multi-center, parallel group study in controls with normal renal function and in patients with mild, moderate and severe renal dysfunction and patients receiving hemodialysis. Up to six subjects in each dose group received peg-interferon a single subcutaneous dose of 1.0 μ/kg .

Results and Conclusions:
Safety. No deaths, serious or severe adverse events were observed. Adverse events moderate to mild in severity typical of Interferon toxicity were observed.

Pharmacology. AUC, Cmax and half-life values were increased in patients with renal impairment compared with controls.

Protocol: C97-058-01
Study Title "SCH 54031: Single Dose Pharmacokinetics of Peg-Interferon Alfa-2b in Young And Geriatric Healthy Volunteers."

Objective. Determine the effect of increased age in the geriatric population on the pharmacokinetics of peg-interferon.

Study Design:

Single-center, single dose, open-label, study in healthy men and women between 20-45 (n=6) and 65-80 (n=18) years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests. A single dose of peg-interferon was administered in the morning and subjects were followed for 168 hours after dosing.

Safety:

One serious adverse event (myocardial infarction) occurred 12 hours after dosing in a 76 year old woman. All subjects experienced at least one adverse event including flu-like symptoms, headache, reductions in neutrophil and platelet counts, increases in systolic and diastolic blood pressure, heart rate and body temperature.

Pharmacology:

No age-related changes were noted in pharmacokinetic parameters.

Conclusions:

Peg-interferon alfa induced serious and non-serious adverse events typical of interferon alfa. After a single dose no age-related changes were noted in pharmacokinetic parameters.

Protocol No. I97-078

Study Title. "SCH 54031: The Effects of Peg-Interferon Alfa-2b on Drug Metabolizing Enzymes in Man".

Study Design:

Single-center, single dose, randomized, open-label, two-way crossover, pharmacokinetic interaction study in 12 healthy men who received an oral CYP450 cocktail of dextromethorphan, caffeine, tolbutamide, dapsone and IV midazolam either with or without peg-interferon alfa-2b (1.0 μg/kg).

Results and Conclusions:

No serious or severe adverse events were observed. Mild to moderate adverse events were observed and were consistent with those induced by alfa interferon. No effects on drug metabolism were seen in normal subjects after a single dose of peg-interferon.

PHASE 3 STUDY

PROTOCOL

Screening Study (Protocol C97-013)

C97-013 is a general protocol entitled "Screening Procedure for Identification of Patients for Participation in Research Protocols Evaluating Agents Alone or in Combination for the Treatment of Chronic Hepatitis C". The objective of this protocol is to screen patients for inclusion in HCV studies. Approximately 1800 subjects were to be screened to enroll 1300 subjects into the phase 3 trial. Patients were required to bring documentation (submitted by referring physician) that they met study inclusion criteria. Patients were assigned a screening number

and underwent history, physical and laboratory examinations, and informed consent procedures at two visits to confirm eligibility for the phase 3 study. Patients eligible for the study were required to have monthly follow-up hematology and biochemistry assessments to monitor their continued eligibility.

Efficacy Study (Protocols C97-010 and I97-010)

Study Title. "Comparison of Polyethylene Glycol-Interferon Alfa-2b (Peg-Intron, SCH 54031) Vs. Interferon Alfa-2b for Treatment of Adult Subjects with Chronic Hepatitis C not Previously Treated with Interferon: Dose Finding Study"

Study Design:

Multi-center (65) active-controlled, randomized, double-blind (with respect to peg-interferon dose) study of efficacy and safety of peg-interferon vs. interferon alfa-2b for the treatment of chronic hepatitis C in approximately 1300 adult subjects not previously treated with interferon. Subjects were randomized (1:1:1:1) to receive peg-interferon (0.5, 1.0, or 1.5 μg/kg SC QW) or interferon alfa-2b ($3x10^6$ SC TIW) administered for 48 weeks. Subjects were followed for 24 weeks after the end of treatment. The study was run under two protocol designations (C97-010 for US sites and I97-010 for sites in Europe and Australia). Data from all sites were combined to prepare a single analysis. Subjects were required to successfully complete the screening protocol in order to be enrolled in the pivotal trial.

Data Safety Monitoring Committee:

An independent committee reviewed safety data in a blinded fashion (blinded to the dose of peg-interferon). On one occasion the dose of peg-interferon was unblinded for the DSMB for 2 subjects with severe thrombocytopenia. As a result the protocol guidelines for the monitoring of platelets were modified.

Study Objectives:

Evaluate the efficacy of peg-interferon alfa-2b compared to interferon alfa-2b with respect to loss of detectable HCV-RNA and normalization of ALT at 24 weeks of therapy (superiority), and at 24 weeks of follow-up (equivalence).

Inclusion Criteria:

Adult (≥18 years) men and women who were serum positive for HCV RNA by quantitative PCR, had a liver biopsy (within 12 months) consistent with chronic hepatitis, had one abnormal ALT within 6 months before screening, and had an elevated ALT (initially or at retest) at the entry visit.

Subjects with compensated liver disease as shown by the following values. Hemoglobin ≥ 12 gm/dl (women) and ≥ 13 gm/dl (men). WBC ≥4,000/mm^3. ANC≥ 1,800/mm^3, platelets ≥130,000/mm^3. Direct and indirect bilirubin, albumin, and serum creatinine WNL.

Subjects with the following acceptable laboratory values. FBS ≤115 mg/dl (non-diabetic). Hemoglobin A 1C ≤ 8.5% (diabetic subjects). TSH normal; ANA ≤ 1:160; HIV, and HBsAg negative.

Alpha fetoprotein had to be normal (within 1 year). Values greater than the upper limit of normal but $\leq$ 50 ng/ml required ultrasound negative for evidence of hepatocellular carcinoma.

Exclusion criteria:
The following were the main exclusion criteria. Previous treatment with interferon or hypersensitivity to interferon; organ transplant recipient; other (non-HCV) causes for the liver disease, advanced liver disease.

The presence of a medical condition that might increase susceptibility to interferon-induced adverse events was grounds for exclusion. The conditions included the following. History of severe psychiatric disorder, especially severe depression, or major psychoses, suicidal ideation and/or suicidal attempt; CNS trauma or active seizure disorders; significant cardiovascular dysfunction or clinically significant ECG abnormalities within 6 months; poorly controlled diabetes mellitus; chronic pulmonary disease; immunologically-mediated disease' potential need of chronic systemic administration of steroids; substance abuse; methadone treatment; clinically significant retinal abnormalities.

Primary Efficacy Outcome:
The primary efficacy outcome was the proportion of patients who responded to treatment. Response to treatment was defined as loss of serum HCV-RNA (<100 copies/ml) and normalization of ALT measured at one time point during treatment (24 weeks of treatment) and at one time point during follow up (6 months post-treatment).

Peg-interferon alfa-2b would be considered efficacious if it was superior to interferon alfa-2b at 24 weeks of treatment or equivalent to interferon alfa-2b at 6 months post-treatment.

Reviewer's comment
The agency did not view the response to treatment at 6 months as sufficient to establish the efficacy of peg-interferon. The agency viewed the analysis of the in-treatment outcome as an interim analysis only.

Secondary Efficacy Outcomes:
The secondary efficacy outcomes included: improvement in Knodell HAI liver biopsy scores (I+II+III) defined as a decrease in the post-treatment score $\geq$2 units from baseline; time to response to treatment; time to relapse.

Efficacy Analyses:
Peg-interferon would be considered efficacious if it was either: a) superior to interferon alfa with respect to the response rate at 24 weeks of treatment (at .025 level of significance, Chi-square test) or b) if it was equivalent to interferon alfa with respect to response rate at 24 weeks post-treatment. Equivalence was defined as the upper limit of a two-sided 97.5% confidence interval (adjusted for

the two analyses) for the difference in response between the treatments being ≤ 12%.

The primary treatment comparison would be the highest dose of peg-interferon alfa (1.5 μg/kg once a week) versus interferon alfa. If the highest dose were to be efficacious then the efficacy of lower peg-interferon doses would be examined.

The primary analysis would be based on all randomized patients who received study drug. Secondary analyses would be based on the data from efficacy-evaluable patients defined as those patients who met key inclusion-exclusion and validity criteria.

Patients with missing data at endpoint would be considered treatment failures.

No covariate adjustments were planned. Association of sustained response rates with baseline and demographic variables, treatment duration and HCV-RNA status would be explored using logistic regression analysis.

Reviewer's comments
The agency agreed that the response to treatment at 6 months' follow-up would be acceptable as the primary efficacy outcome of the study. However the agency and the sponsor did not reach agreement on the criteria for establishing equivalence between peg-interferon and interferon. The agency found a Δ of 15% absolute to be unacceptable and believed that the estimate of response for interferon alfa (30%) was unrealistically high. The agency also believed that the use of the highest peg-interferon dose as the primary efficacy comparison group was risky given the unknown safety profile of the new drug.

The agency agreed to filing the data, despite the absence of a clear and prospectively defined analytical plan, after the sponsor presented unblinded efficacy data supporting the superiority of the two peg-interferon top doses to interferon. The agency reiterated its previously expressed concerns about the lack of a confirmatory study and about the size of the safety database for the new drug.

Secondary Efficacy Analyses:
The following secondary outcomes: improvement in biopsy histology compared to pre-treatment (based on the sum of Knodell Scores for inflammation and necrosis), time to response, and time to relapse would be summarized and presented by treatment group.

Sample Size Calculations:
It was assumed that the response rate at 24 weeks of treatment for the interferon treatment group would be 50%. A sample size of 325 patients per treatment group would be sufficient to detect a 13% difference in the response rates between treatments with at least 80% power (significance level = 0.025, two-sided test).

It was also assumed that the response rate at 24 weeks of follow-up for the interferon and peg-interferon groups would be 25%. A sample size of 325 subjects would have at least a 90% probability of fulfilling the equivalence criterion.

Interim Analysis:
No formal interim analysis would be performed. However an analysis of the first primary efficacy endpoint was planned midway through the study when all patients had completed 24 weeks of treatment.

Safety Analyses:
Adverse experiences and laboratory parameters would be summarized by treatment group. The treatment groups would be compared with respect to the distribution of severity scores (absent, mild, moderate, severe) for flu-like symptoms and psychiatric disorders. A Kruskal-Wallis test would be used to test for overall treatment differences. If this test were to be significant (alpha = 0.05), pairwise comparisons of the treatment groups would be made using a Wilcoxon test (each at a nominal level of 0.05).

Subject Discontinuation Criteria:
A subject could be removed from the study for any of the following reasons: serious or life-threatening adverse event; investigator's or subject's choice; subject's lack of compliance. Subjects discontinued for adverse events were to be followed medically until the adverse event resolved or stabilized and were then followed for 24 weeks post-discontinuation.

Modifications of Study Treatment:
Severe (Grade 3) Adverse Events
Dose of study drug was reduced until the severe adverse event returned to mild ($\leq$ grade 1), when the full dose was resumed. If adverse event persisted despite the reduced dose, treatment was interrupted up to a maximum of two weeks. After resolution of the adverse event, treatment resumed at reduced doses. If these doses were tolerated for at least two weeks, dosing increased to the full protocol dose. If the adverse event recurred the subject could be maintained at the reduced doses or be discontinued from treatment.

Life-Threatening (Grade 4) Adverse Events
Study drug was to be discontinued permanently. Follow-up would be scheduled as needed or in a maximum of two weeks. Patients with grade 4 flu-like symptoms were exempted from this rule (see below).

Subjects with Grade 4 Flu-like Symptoms
Treatment was to be interrupted up to a maximum of two weeks until the adverse event returns to $\leq$ grade 1. Treatment could be restarted at the reduced doses. If the reduced doses were tolerated for at least two weeks, dosing could be increased to the full protocol dose. If the adverse event recurred the subject could be maintained at the reduced dose or could be discontinued from the study.

Subjects with decreased platelet counts
The following guidelines were adopted.

For counts <100,000/mm^3. Recount every two weeks until count > 100,000.

For counts <80,000/mm^3. Reduce study drug by half and recount within one week. Return to full dose if count >100,000/mm^3 for 4 weeks and recount every two weeks for four weeks.

For counts <50,000/mm^3. Discontinue study drug and monitor patients until platelet counts normalize without medication.

Grading of Adverse Events Severity:
A modified WHO grading system was used. For adverse events not covered by the grading system, the following definitions were used. *Mild*: easily tolerated. *Moderate*: interferes with usual activity and may require intervention. *Severe*: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention. *Life-threatening*: immediate risk of death.

Monitoring:
Evaluations During Treatment
The following evaluations were scheduled for weeks 2, 4, 8, 12, 18, 24, 30, 36, 42, 48 Vital signs, body weight, hematology, adverse events, concurrent illnesses, concomitant medications, documentation of date and time of the last dose of study drug.

The following evaluations were scheduled for the following visits. Quality of Life (SF-36, self-administered) and physical exam including GI/liver (weeks 12, 24, 36, 48). Blood chemistry (complete at weeks 12, 24,36, 48; abbreviated at other visits). TSH (weeks12, 24, 36, 48).

Chest X-ray, ECG, eye exam were performed when clinically indicated.

Evaluations During Follow-up
The following evaluations were scheduled for weeks 4, 12 and 24: vital signs, body weight, adverse events, concurrent Illnesses, concomitant medications, hematology. Quality of Life, physical exam including GI exam, and TSH were done at weeks 12 and 24). A complete set of blood chemistry was measured at week 12 and 24, and an abbreviated set at week 4. Finally a liver biopsy was performed between week 24 and 26.

Efficacy Parameters
Serum HCV-RNA testing was performed by a central laboratory

[redacted] at baseline and at treatment weeks 4, 12, 24, 36, 48 and follow-up weeks 4, 12 and 24. ALT levels were measured at treatment weeks 2, 4, 8, 12, 18, 24, 30, 36, 42, 48 and follow-up weeks 4, 12 and 24.

Efficacy time-points were defined using the following range of days. *Baseline*: on-or-before treatment day 1. *Week 48*: between treatment days 309-364. *End of Treatment*: stop date $\pm$ 2 weeks. *Follow-up Weeks 12 and 24* were respectively defined as follow-up days 57-112, and days 141-196.

Liver biopsies were graded using the Knodell HAI score. The first 3 categories (I+II+III) of the score are used to grade necrosis and inflammation and the fourth category (IV) is used to stage fibrosis and cirrhosis. The pathologist was blinded to the patient number, treatment group and timing of the biopsy (pre or post-treatment).

Quality of Life was assessed using the self-administered short form (SF)-36. This HQL instrument evaluates eight domains: physical functioning, physical role, bodily pain, general health perceptions, vitality, social functioning, role emotional, and general mental health. These eight domains are summarized into a physical component summary score and a mental component summary score.

Neutralizing Antibodies
Measurements were performed at entry and at week 4 post-treatment.

Pharmacokinetic measurements
Peg-interferon levels were measured at weeks 4, 12, 24, 36, 48 of treatment and at week 4 post-treatment. Please see the pharmacology review for a discussion of these results.

Amendments to the Efficacy Protocol
The first amendment changed the primary efficacy variable from a loss of serum HCV RNA to a composite of ALT normalization and loss of detectable serum HCV-RNA at 24 weeks of treatment and included additional statistical tests to compare the safety profile of PEG-Intron with interferon alfa-2b.

A second amendment included the following changes: decreased number of study centers from 65 to 55; increased sample size from 1000 to 1300; changed the criteria for determination of effectiveness by setting the upper limit of a 97.5% CI for the difference between treatments from $\leq$15 to $\leq$12% difference compared to control; set specific rules for monitoring platelet counts; added detail to the analysis plan for health-related quality of life. Finally the amendment broadened the inclusion criteria with respect to ALT levels. Abnormal ALT would be required once within 24 weeks of entry (instead of twice within 10 weeks of entry) and at entry on one of two measurements (no ALT retest was allowed previously).

CONDUCT OF THE STUDY

Clinical Study Centers

Fifty-three study centers in the US, Europe, and Australia participated in the study. Centers located in the US enrolled nearly two thirds of the total number of patients (see Table 2).

Table 2. Number of Study Patients and Study Centers

Location of Center	Number of Centers	Number of Patients
US	33	767
Germany	4	132
France	5	117
Spain	3	63
Greece	2	50
Austria	1	27
Switzerland	2	25
UK	1	7
Australia	2	36

Study Eligibility

A number of non-eligible patients were enrolled in the study. Table 3 shows the number of major violations of chemistry, hematology and liver biopsy enrollment criteria by treatment group. Violations included: missing quantitative PCR at baseline, normal ALT, high or low TSH, elevated glucose level, elevated or missing Hba1c, elevated bilirubin, low WBC or platelets, and liver biopsy obtained more than 1 year before entry in the study.

Table 3. Violation of Protocol Enrollment Criteria

	PCR	ALT	Liver Biopsy	Clinical Chemistry and Hematology
PEG-IFN 0.5 µg/kg	1	0	11	56
PEG-IFN 1.0 µg/kg	0	2	6	51
PEG-IFN 1.5 µg/kg	1	1	9	43
IFN 3×10^6 U	1	2	6	65

Treatment Allocation and Study Completion

Table 4 shows the number of patients allocated to each treatment group and the number of patients (and percentages) completing the treatment and follow-up periods. In the study a total of 1224 patients was randomized and a total of 1219 patients was treated. Nearly 80% of patients completed treatment and follow up.

One-hundred-twenty-four patients were screened but were not enrolled in the study.

Table 4. Treatment Allocation and Study Completion

	Peg-Interferon α Treatment Groups			Interferon α $3x10^6$ U
	0.5 μg/kg	1 μg/kg	1.5μg/kg	
Randomized	315	298	304	307
Completed Treatment	266 (84%)	241 (81%)	247 (81%)	240 (78%)
Completed Follow up	255 (81%)	229 (77%)	228 (75%)	231 (75%)

Withdrawals from Study Treatment

The percentage of patients withdrawn from treatment was similar (around 20%) in the four treatment groups (see Table 5). In the 1.0 μg/kg peg-interferon group the percentage of withdrawals due to adverse events appeared to be higher (12%) and the percentage of withdrawals due to treatment failure appeared to be lower (<1%) compared to the interferon-treated group (6% and 5% respectively).

Table 5. Number of Patients Withdrawn during the Treatment Period and Reason for Withdrawal

Reason for withdrawal	Peg-IFN 0.5μg/kg	Peg-IFN 1.0 μg/kg	Peg-IFN 1.5 μg/kg	IFN $3x10^6$ U
Death	1 (0.3)[a]	0	0	1 (0.3)
Other Adverse Events	28 (9)	36 (12)	30 (10)	18 (6)
Treatment Failure	10 (3)	2 (0.7)	5 (2)	14 (5)
Loss to Follow up	4 (1)	3 (1)	3 (1)	5 (2)
Subject's Decision	4 (1)	8 (3)	12 (4)	9 (3)
Non-compliance	2 (1)	7 (2)	7 (2)	16 (5)
TOTAL	49 (16)	56 (19)	57 (19)	63 (21)

[a]Numbers in parentheses are percentages.

Treatment Compliance

Compliance of patients with study treatment was reasonable. Across treatment groups 81-87% percent of study medication dosages were taken.

DEMOGRAPHICS

The demographic and baseline disease characteristics of study patients were generally balanced across study groups. The principal characteristics are shown in Table 6.

Table 6. Demographics and Baseline Disease Characteristics of Study Patients

		PEG-Interferon α-2b			Interferon α-2b
		0.5 μg/kg	1.0 μg/kg	1.5 μg/kg	3 x10^6 U
Age	**years**[a]	43	44	43	43
Gender:	**women**	130 (41%)	109 (37%)	114 (38%)	96 (32%)
	men	185 (59%)	188 (63%)	190 (63%)	207(68%)
Ethnicity:	**Caucasian**	283 (90%)	270 (91%)	286 (94%)	270(89%)
	African-American	15 (5%)	17 (6%)	11 (4%)	16 (5%)
	Hispanic	10 (3%)	5 (2%)	3 (1%)	11 (4%)
	Asian	4 (1%)	5 (2%)	4 (1%)	5 (2%)
HCV Genotype:	**1**	212 (67%)	199 (67%)	223 (73%)	217(72%)
	2	35 (11%)	30 (10%)	32 (11%)	28 (9%)
	3	53 (17%)	53 (18%)	41 (14%)	53 (18%)
	4	8 (3%)	12 (4%)	4 (1%)	3 (1%)
	5	2 (<1%)	1 (<1%)	0	0
	6	0	0	1 (<1%)	1(<1%)
	N.D.	5 (2%)	2 (0.7%)	3 (1%)	1 (<1%)
HCV RNA:	**copies/ml <2x10^6**	83 (26%)	72 (24%)	83 (27%)	75 (25%)
	>2x10^6	231 (73%)	225 (76%)	220 (72%)	227(75%)
ALT:	**x ULN**[b]	2.3 (0.6 -16)	2.2 (1.0 -11)	2.3 (0.5 -10)	2.3 (0.7-11)

[a] Numbers are means.
[b] Upper Limit of Normal; numbers are medians; numbers in parentheses are ranges.

The mean age of study patients was 43 years and ranged from 18 to 73 years. Approximately two thirds of study patients were men and 90% of the patients were Caucasians. Approximately 70% of patients were infected with HCV genotype 1 and 75% of patients had high levels of HCV RNA in the circulation (>2x10^6/ml serum). These two factors are associated with less favorable treatment outcome. The incidence of these two unfavorable prognostic factors in

the study patients is consistent with the incidence in the US population affected by HCV. Elevations in ALT levels at baseline were comparable across treatment groups; median ALT levels were 2-fold greater than the upper limit of normal (see Table 6).

The route of HCV infection was parenteral in roughly 50% of study patients, transfusion-associated in 20%, and sporadic in 30% of patients. The mean duration of infection was approximately 20 years with a range of <1 to 58 years. Liver biopsies were available at baseline in about 90% of study patients. The mean score for hepatic inflammation and necrosis (sum of Knodell scores I, II, and III) was 7 and the mean score for hepatic fibrosis (Knodell score IV) was 1.4. Approximately 14% of patients had bridging fibrosis of hepatic lobules, and 4% of patients had frank cirrhosis.

PRIMARY EFFICACY OUTCOME

Treatment Response

Treatment response was defined as loss of serum HCV RNA (limit of detection 100 copes/ml) and normalization of ALT at 6 months after the end of the treatment period. Table 7 shows that the response rates to peg-interferon 1.0 μg/kg and 1.5 μg/kg doses were similar and were superior to response rates to interferon alfa. The response rate to peg-interferon 0.5 μg/kg was intermediate between the response to 1.0 and 1.5 μg/kg peg-interferon and the response to $3x10^6$ U interferon.

There was no requirement for minimum duration of loss of HCV RNA detection. However for nearly all treatment responders the loss of HCV RNA detection occurred during the treatment period and was sustained. Ninety-six percent of subjects (228/238) with undetectable HCV RNA at endpoint also had normal ALT. However only between 70 and 85% of subjects in the various treatment groups who had normal ALT also had non-detectable viral RNA by the endpoint. Therefore ALT normalization alone overestimated virologic response to treatment by 15-30% (see Table 7).

Table 7. Rates of Response to Treatment

	PEG-Intron 0.5 μg/kg (N=315)	PEG-Intron 1.0 μg/kg (N=298)	PEG-Intron 1.5μg/kg (N=304)	INTRON A $3 x10^6$ U (N=307)	Difference between PEG-Intron 1.0 μg/kg and INTRON A
Treatment Response (Virologic Response and ALT Normalization)	17%	24%	23%	12%	11 (5, 18)[a]
• Virologic Response[b]	18%	25%	23%	12%	12 (6, 19)
• ALT Normalization	24%	29%	28%	18%	11 (5, 18)

[a] Numbers in parentheses are the 95% Confidence Interval.
[b]Serum HCV RNA was measured by a research-based quantitative polymerase chain reaction with a lower limit of detection of 100 copies/ml at the National Genetics Institute, Culver City, CA.

Patients with missing data at endpoint (24 weeks post-treatment) were considered treatment failures for the purpose of the efficacy analysis. Review of available HCV RNA measurements in patients with missing data at endpoint suggested that a few of these patients might have been treatment responders. The numbers however would not have significantly raised the estimate of treatment response.

Peg-interferon alfa-2b (1.0 μg/kg) was superior to interferon alfa-2b in various subgroups including subject's gender, age, and body weight, and in various disease characteristics including source of HCV infection, duration of HCV infection, HCV genotype, HCV RNA titers in plasma, and liver histopathology. Response to treatment was consistent across continents and across individual study centers.

Long term studies are needed to determine what proportion of treatment responders achieve cure (viral eradication). Studies are also needed to demonstrate that virologic cure can halt the progression of chronic hepatitis C and prevent the development of cirrhosis, hepatocellular carcinoma and other associated complications.

Decreased Titers of HCV RNA

Figures 1 and 2 show the effects of interferon treatment on viral titers.

Figure 1. HCV RNA (Means) During Treatment and Follow-Up by Treatment Group

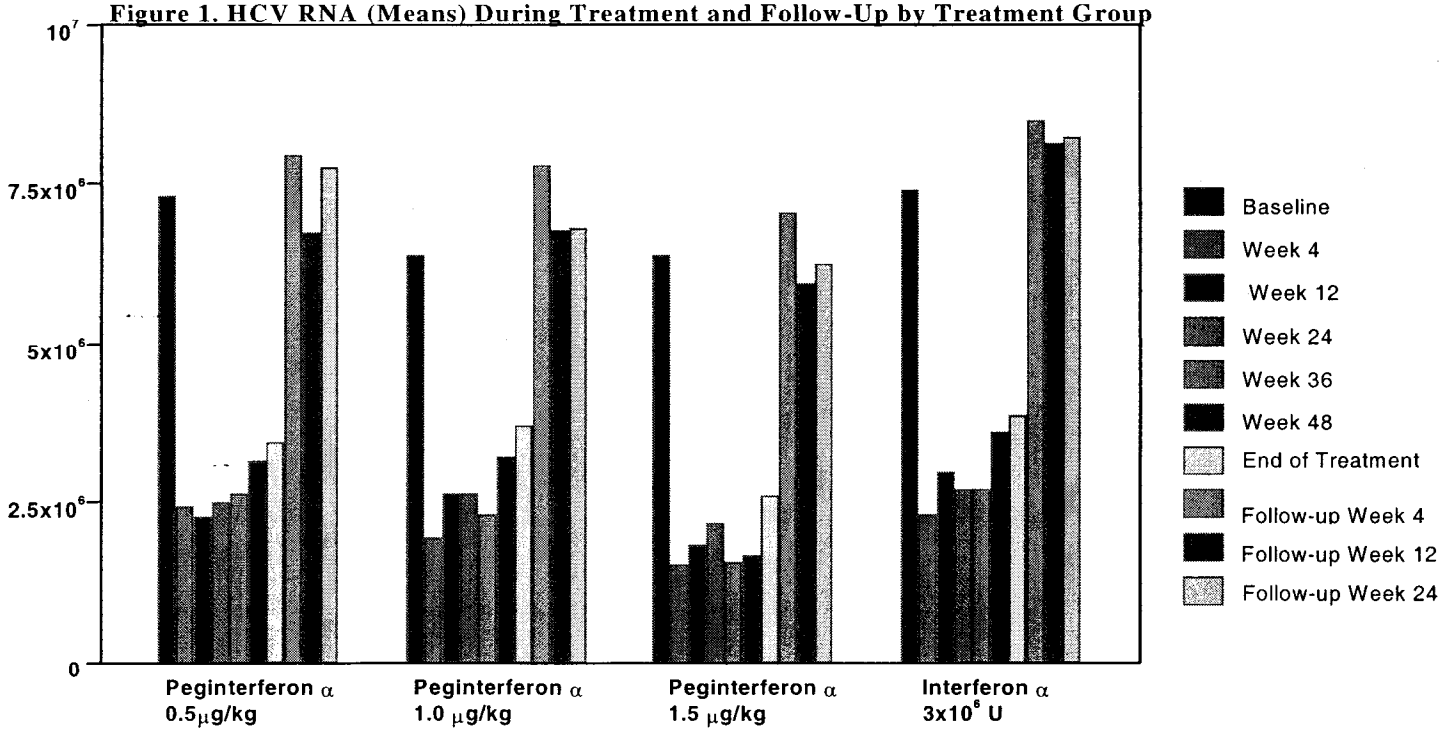
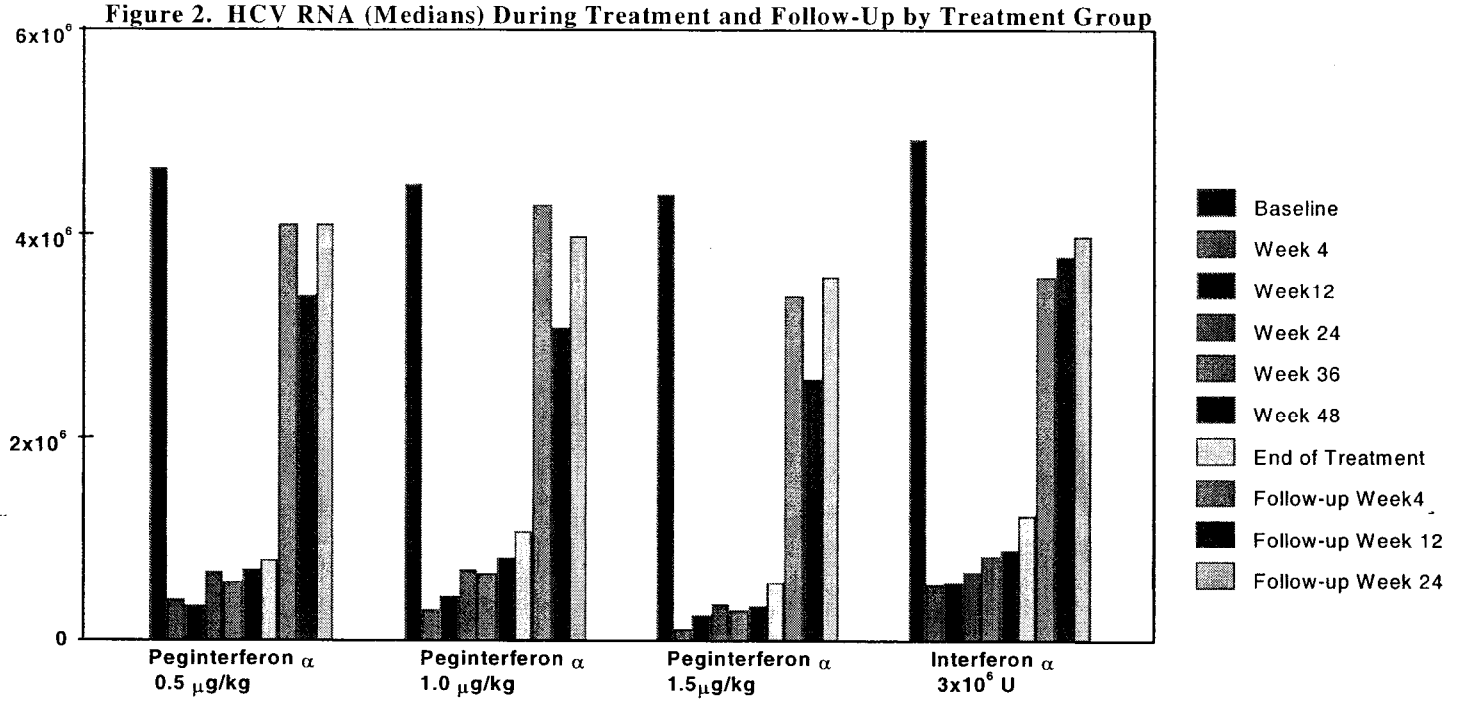


Figure 2. HCV RNA (Medians) During Treatment and Follow-Up by Treatment Group



During the treatment period the mean (Figure 1) and median (Figure 2) viral titers decreased and appeared to return towards baseline by the fourth week after the end of treatment. These decreases appeared to be greater in the two highest peg-interferon groups. In nearly all patients, irrespective of response to treatment, the circulating levels of HCV RNA decreased during the treatment period. This indicates that inhibition of viral replication during interferon treatment occurred even in patients who did not achieve viral eradication.

Temporary Loss of HCV RNA Detection during Treatment

In a few patients (around 5% in each group) HCV RNA disappeared temporarily from the circulation only to reappear during the treatment period. Reappearance of HCV RNA in these patients was considered evidence of breakthrough infection. There was little or no evidence of fluctuation in HCV RNA status from positive to negative either during the treatment period or the follow up period.

SECONDARY EFFICACY OUTCOMES

Liver Histopathology

Interferon treatment induced very modest decreases from baseline in hepatic inflammation and necrosis as measured by Knodell scoring of liver biopsies. The decreases in score were not different between treatment groups. Across all groups the mean score post-treatment was numerically lower (-1.5) compared to the score at baseline. Nearly 50% of all patients with available paired liver biopsies were judged to show some improvement in the post-treatment biopsy (see Table 8). The number of patients with missing data was high (about 40%).

Table 8. Effect of Treatment on Hepatic Inflammation and Necrosis [Knodell HAI (I+II+III)]

Histology[a]	PEG-Intron 0.5 μg/kg (N=198)	PEG-Intron 1.0 μg/kg (N=178)	PEG-Intron 1.5 μg/kg (N=177)	Interferon alfa-2b 3 x10^6 U (N=191)
Improved	97 (49)	89 (50)	85 (48)	90 (47)
No change	64 (32)	57 (32)	56 (32)	60 (31)
Worse	37 (19)	32 (18)	36 (20)	41 (21)

[a] Improved is a change from pre- to post-treatment in the Knodell HAI score for inflammation (I+II+III) categorized as a decrease of ≥2; no change is a change of -1 to 1; and worse is an increase of ≥2.

The assessment of liver fibrosis using Knodell scoring shows that mean/median changes in scores from baseline were equal or nearly equal to 0 in all treatment groups. Categorical analysis of the fibrosis data showed that most patients did not change their score from baseline; moreover the number of patients with improved scores was similar to the number of patients with worsened scores.

Time to Treatment Response

There was no difference between groups in the time to treatment response defined as time to first achieving a sustained loss of detection of HCV RNA (see Table 9). Most of the patients with long-term virologic response had undetectable HCV RNA levels by 6 months. As shown in Table 9 in the different groups between 94 and 100% of responders had become HCV RNA negative by week 24 of the treatment period. Table 9 also shows that the earlier the apparent loss of HCV RNA, the greater the chance that the loss of detectable HCV RNA would be sustained.

Table 9. Time to Virologic Response

Time of First Neg. HCV-RNA	PEG-Intron 0.5 μg/kg (N=57)[a]	PEG-Intron 1.0 μg/kg (N=73)	PEG-Intron 1.5 μg/kg (N=71)	Interferon alfa-2b 3 x10^6 U (N=37)
Week 4	26/32[b] (81)[c]	33/39 (85)	46/60 (77)	18/21 (86)
Week 12	20/42 (48)	31/60 (52)	19/60 (32)	15/41 (37)
Week 24	7/35 (20)	4/31 (13)	5/33 (15)	4/23 (17)
Week 36	1/10 (10)	1/8 (13)	0/15	0/4
Week 48	3/8 (38)	4/9 (44)	0/6	0/4
FU week 12	0/0	0/0	1/1	0/0

[a]Total number of virologic responders (negative HCV RNA at FU week 12) in each group.
[b]Numerator is the number of subjects who first became HCV RNA negative and remained negative at endpoint. Denominator is the number of all HCV RNA negative subjects (including relapsers).
[c]The numbers in parentheses are percentages.

Time to Relapse

The time to virologic relapse was not different between groups. A large proportion of patients (41-54% across treatment groups) with undetectable serum HCV RNA by the end of 12 months of treatment had detectable HCV RNA by six months after the end of treatment. Virologic relapse occurred primarily during the first four weeks of the post-treatment period (see Table 10). The rates of relapse were highest in patients with type 1 genotype and with high viral numbers at baseline.

Table 10. Proportion of Responders at End of Treatment who Relapse during the Post-treatment Period

	Peg-interferon alfa Treatment Groups			Interferon alfa $3x10^6$ U
	0.5 μg/kg	1.0 μg/kg	1.5 μg/kg	
Treatment Responders	105 (100%)	121(100%)	149 (100%)	73 (100%)
Post-treatment Relapsers				
Week 0-4	38 (36%)	45 (37%)	70 (47%)	34 (36%)
Week 12	8 (8%)	1 (1%)	6 (4%)	3 (4%)
Week 24	3 (3%)	4 (3%)	4 (3%)	1 (1%)

Health-Related Quality of Life

The hypothesis to be tested was that interferon treatment improves HQL in particular vitality during the post-treatment period compared to baseline. The SF36 was used to assess the following eight domains of health physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and general mental health. Each of the domains was scored separately and converted to a scale ranging from 0 (worst score) to 100 (best score). The pre-specified primary comparison was between the peg-interferon 1.5 μg/kg and the interferon groups between baseline and follow up at 12 and 24 weeks using a repeated measurement model; the vitality domain was of primary interest.

Analyses showed no differences between any of the groups either numerically or statistically. All the scores in all the groups deteriorated during the treatment

period and tended to returned to baseline in the post-treatment period.

RESPONSE TO TREATMENT BY GENDER, ETHNIC GROUP AND AGE

Women made up 37% of the sample size. No gender differences were seen on response to interferon treatment (see Table 11). Effects of race on response to interferon treatment cannot be determined from this study because 91% of study subjects were of Caucasian origin. African American and Hispanics tended to have lower response rates and Asians higher response rates compared to Caucasians (see Table 11). However these differences appeared to be related to differences in prognostic variables at baseline in the different groups (see Table 12).

Table 11. Response to Treatment by Gender and Ethnic Subgroups

	Women		Men		Caucasian		African American		Hispanic		Asian	
Treatment	N[a]	Resp[b]	N	Resp	N	Resp	N	Resp	N	Resp	N	Resp
Peg 0.5 µg/kg	130	23(18)	185	29(14)	283	47(17)	15	2(13)	10	1(10)	4	2(50)
Peg 1.0 µg/kg	109	26(24)	189	44(23)	271	65(24)	17	2(12)	5	0	5	3(60)
Peg 1.5 µg/kg	114	31(27)	190	38(20)	286	64(22)	11	2(18)	3	0	4	3(75)
IFN 3x10[6] Units	97	13(13)	210	24(11)	273	36(13)	16	0	12	0	5	1(20)
Peg groups[c]	353	80(23)	564	111(20)	840	287(34)	43	6(14)	18	1(5)	13	8(61)

[a] Number of patients in each subgroup.
[b] Number of patients who responded to treatment; the percentages are shown in parentheses.
[c] Combined data from the three peg-interferon treatment groups.

Table 12 shows that in this study the occurrence of infection with HCV genotype 1 (an unfavorable prognostic criterion) was similar in men and women. However compared to Caucasians the occurrence of genotype 1 was higher in African Americans and Hispanics and lower in Asians.

Table 12. Distribution of HCV Genotype in Gender and Ethnic Subgroups

HCV Genotype	Men	Women	Caucasian	African American	Hispanic	Asian	Other
Genotype 1	528(69)[a]	317(70)	767(69)	54(91)	25(83)	5(35)	3
Genotype 2-6	230(30)	128(28)	335(30)	5(9)	5(17)	11(69)	1
Undeter-mined	6	5	10	0	0	1	0

[a]Numbers in parentheses are percentages.

Clinical studies of PEG-Intron did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects (see Table 13). Response rates appeared to be numerically higher in younger subjects. No pediatric subjects were included in this study.

Table 13. Proportion of Responders by Age and by Treatment Group

Age	Treatment Group	
	Peg IFN[a]	IFN
≤35 years	29-47% (N=145)	17% (N=53)
36-65years	15-22% (N=547)	8% 11% (N=243)
>65 years	0-14% (N=20)	14% (N=7)

[a] In the Peg-IFN group the numbers (%) represent the range of response rates in the three dose groups

RESPONSE TO TREATMENT BY DISEASE-RELATED FACTORS

HCV Genotype and Plasma Titers

Logistic regression analyses showed that HCV genotype other-than 1 and levels of circulating HCV RNA $\leq 2x10^6$ were significantly associated with favorable response to treatment. The data suggests that duration of infection does not influence treatment response.

Across all treatment groups viral genotype and high plasma viral numbers were associated with lower response to treatment as shown in Table 14.

Table 14. Proportion of Responders by Viral Genotype and by Plasma Viral Numbers

	Peg-IFN α			IFNα
	0.5μg/kg	1μg/kg	1.5μg/kg	$3x10^6$ U
Genotype 1				
$\leq 2x10^6$	14/52 (27%)	16/42 (38%)	19/56 (34%)	10/48 (21%)
$>2x10^6$	8/159 (5%)	12/157(8%)	12/167(7%)	4/169(2%)
Genotypes 2-6				
$\leq 2x10^6$	16/30 (53%)	17/29 (58%)	18/26 (69%)	9/27 (33%)
$>2x10^6$	17/68 (25%)	26/67 (39%)	21/52 (40%)	14/58 (24%)

The route of HCV infection and the duration of the infection did not appear to influence the response to treatment.

Liver Fibrosis

Few study patients had advanced stages of liver fibrosis (cirrhosis or bridging fibrosis) at baseline. Response to treatment in these patients was lower compared to overall response rates. The apparent association of advanced liver fibrosis with lower response was seen in all treatment groups (see Table 15).

Table15. Treatment Response Rates in Patients with Liver Fibrosis

	Peg-IFN α			IFNα
	0.5μg/kg	1.0μg/kg	1.5μg/kg	3x10^6 U
Cirrhosis	0/9	1/9 (11%)	0/12	1/13 (8%)
Bridging Fibrosis	6/51 (12%)	6/40 (15%)	4/35 (11%)	2/38 (5%)

Treatment Response by Treatment Duration and Duration of Dose Reduction

Response rates appeared to be very low in patients who received less than 40 weeks of treatment. Dose reductions lasting for 4 weeks or less appeared to have little or no impact on treatment response. The effect of longer dose-reductions showed no consistent trends across treatment groups due to low number of patients in these subgroups.

SAFETY OUTCOMES

Serious and Life-Threatening Adverse Events

Incidence of Serious Events across Treatment Groups

The occurrence of deaths and life-threatening adverse events did not appear to be dose-dependent. The incidence of serious adverse events overall was similar (about 12%) in all treatment groups. The body systems involved and the clinical manifestations of the serious adverse events were similar across groups.

Deaths

There was one patient death, a suicide, among patients receiving peg-interferon and two patient deaths in the interferon group (one murder/suicide and one sudden death).

Life-threatening Adverse Events

Two life-threatening adverse events (gastroenteritis and suicidal ideation) were reported in the interferon alfa-treated group. Six life-threatening events (two cases of neutropenia, one case each of depression, drug abuse, accidental injury, and neoplasm) were reported in the peg-interferon groups.

Other Serious Adverse Events

The highest incidence of serious adverse events among all organ systems

occurred in the neuropsychiatric category (about 2% in each treatment group). Serious adverse events in other body systems occurred at a frequency ≤1%. The individual types of serious adverse events included: suicide attempt, suicidal ideation, severe depression; relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, retinal ischemia, retinal vein thrombosis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (pneumonia, abscess); autoimmune thrombocytopenia, hyperthyroidism, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, aggravated psoriasis; urticaria. Additional details of these events are provided in the narratives of serious adverse events.

Adverse Events (All Grades)

Incidence of Adverse Events across Treatment Groups

Patients receiving PEG-Intron appeared to experience a greater number of adverse events compared to patients receiving INTRON A. This difference was due primarily to a greater number of adverse events in patients receiving the higher PEG-Intron dosages (See Table 16).

Table 16. Adverse Events (All Grades) by Treatment Group

	PEG-INTRON			INTRON A
	0.5 μg/kg	1.0 μg/kg	1.5 μg/kg	$3x10^6$ U
Application Site Disorders	**150 (48)**	**143 (48)**	**138 (45)**	**64 (21)**
Injection Site Inflammation	139 (44)	126 (42)	123 (40)	49 (16)
Injection Site Pain	16 (5)	7 (2)	8 (3)	4 (1)
Injection Site Reaction	23 (7)	30 (10)	29 (10)	16 (5)
Autonomic Nervous System Dis.	**45 (14)**	**52 (18)**	**63 (21)**	**51 (17)**
Mouth Dry	13 (4)	13 (4)	24 (8)	13 (4)
Sweating Increased	23 (7)	17 (6)	29 (10)	21 (7)
Body as a Whole - General Dis.	**283 (90)**	**277 (93)**	**290 (95)**	**272 (90)**
Asthenia	38 (12)	35 (12)	45 (15)	33 (11)
Chest Pain	24 (8)	18 (6)	14 (5)	12 (4)
Erythema	15 (5)	15 (5)	12 (4)	8 (3)
Fatigue	137 (43)	151 (51)	138 (45)	152 (50)
Fever	99 (31)	133 (45)	133 (44)	91 (30)
Headache	191 (61)	190 (64)	194 (64)	175 (58)
Influenza-Like Symptoms	57 (18)	65 (22)	76 (25)	59 (19)
Malaise	19 (6)	25 (8)	24 (8)	21 (7)
Rigors	106 (34)	120 (40)	134 (44)	99 (33)
RUQ Pain	39 (12)	23 (8)	27 (9)	24 (8)
Weight Decrease	30 (10)	34 (11)	65 (21)	39 (13)
CNS and PNS Disorders	**84 (27)**	**91 (31)**	**101 (33)**	**91 (30)**
Dizziness	26 (8)	36 (12)	42 (14)	30 (10)
Hypertonia	12 (4)	15 (5)	12 (4)	8 (3)
Hypoesthesia	10 (3)	6 (2)	14 (5)	9 (3)
Paresthesia	14 (4)	10 (3)	18 (6)	13 (4)
Endocrine Disorders	**15 (5)**	**21 (7)**	**22 (7)**	**13 (4)**

Hypothyroidism	8 (3)	16 (5)	14 (5)	8 (3)
Gastrointestinal System Disorders	**168 (53)**	**180 (61)**	**198 (65)**	**174 (57)**
Abdominal Pain	44 (14)	44 (15)	41 (13)	34 (11)
Anorexia	31 (10)	58 (20)	77 (25)	50 (17)
Diarrhea	51 (16)	54 (18)	60 (20)	47 (16)
Dyspepsia	16 (5)	18 (6)	19 (6)	20 (7)
Nausea	66 (21)	77 (26)	75 (25)	61 (20)
Toothache	8 (3)	8 (3)	12 (4)	16 (5)
Vomiting	15 (5)	22 (7)	24 (8)	19 (6)
Liver and Biliary System Disorders	**21 (7)**	**23 (8)**	**15 (5)**	**15 (5)**
Hepatomegaly	20 (6)	17 (6)	11 (4)	14 (5)
Musculoskeletal System Disorders	**213 (68)**	**217 (73)**	**231 (76)**	**208 (69)**
Arthralgia	83 (26)	74 (25)	94 (31)	81 (27)
Myalgia	150 (48)	160 (54)	186 (61)	161 (53)
Psychiatric Disorders	**182 (58)**	**168 (57)**	**172 (57)**	**177 (58)**
Agitation	17 (5)	7 (2)	10 (3)	6 (2)
Anxiety	30 (10)	27 (9)	22 (7)	31 (10)
Concentration Impaired	30 (10)	31 (10)	31 (10)	24 (8)
Depression	84 (27)	85 (29)	83 (27)	75 (25)
Emotional Lability	16 (5)	16 (5)	15 (5)	19 (6)
Insomnia	53 (17)	68 (23)	60 (20)	69 (23)
Irritability	60 (19)	52 (18)	52 (17)	74 (24)
Nervousness	17 (5)	13 (4)	14 (5)	8 (3)
Somnolence	8 (3)	11 (4)	21 (7)	17 (6)
Reproductive Disorders, Female	**21 (16)**	**12 (11)**	**21 (18)**	**9 (9)**
Dysmenorrhea	7 (5)	3 (3)	8 (7)	2 (2)
Menorrhagia	5 (4)	2 (2)	7 (6)	2 (2)
Menstrual disorder	10 (8)	4 (4)	7 (6)	3 (3)
Resistance Mechanism Disorders	**81 (26)**	**59 (20)**	**63 (21)**	**61 (20)**
Infection Viral	40 (13)	33 (11)	27 (9)	30 (10)
Respiratory System Disorders	**120 (38)**	**109 (37)**	**116 (38)**	**84 (28)**
Coughing	23 (7)	19 (6)	25 (8)	15 (5)
Dyspnea	18 (6)	11 (4)	18 (6)	6 (2)
Pharyngitis	37 (12)	30 (10)	21 (7)	21 (7)
Sinusitis	32 (10)	20 (7)	28 (9)	20 (7)
Upper Resp Tract Infection	16 (5)	10 (3)	5 (2)	10 (3)
Skin and Appendages Disorders	**138 (44)**	**133 (45)**	**168 (55)**	**126 (42)**
Alopecia	64 (20)	66 (22)	104 (34)	67 (22)
Pruritus	27 (9)	37 (12)	31 (10)	23 (8)
Rash	26 (8)	19 (6)	25 (8)	20 (7)
Skin Dry	21 (7)	33 (11)	31 (10)	26 (9)
Vision Disorders	**28 (9)**	**33 (11)**	**46 (15)**	**37 (12)**
Conjunctivitis	12 (4)	12 (4)	18 (6)	7 (2)

The incidence of adverse events in each Body System was numerically greater in two highest peg-interferon groups compared to the incidence in the interferon group. In absolute terms the difference ranged from –1% to +27% (see Table 16).

The incidence of individual adverse events within each Body System was also generally greater in the two highest peg-interferon groups compared to the interferon group (See Table 16). A listing of individual adverse events showing noteworthy differences between treatment groups is provided below. In this listing the incidence in the two highest peg-interferon groups is cited first and is contrasted with the incidence in the interferon group. The adverse events are: inflammation (40-42% for PEG-IFN vs. 16% for IFN) and pain (2-3% for PEG-IFN vs. 1% for IFN) at the drug application site; fever (44-45% vs. 30%) and rigors (40-44% vs. 33%); hypothyroidism (5% vs. 3%); anorexia (20-25% vs. 17%); diarrhea (18-20% vs. 16%); nausea (25-26% vs. 20%); myalgia (54-61% vs.53%); dysmenorrhea (3-7% vs. 2%); dyspnea (4-6% vs. 2%); alopecia (22-34% vs. 22%); and conjunctivitis (4-6% vs. 2%). See also Table 16.

Most Common Adverse Events

The most common adverse events are shown in Table 17 for the 1.0 μg/kg peg-interferon dose group and for the interferon group. Headache, fatigue, musculoskeletal pain, and "flu-like" symptoms occurred in approximately 50% of patients. Fever and rigors occurred in about 20% of patients. Application site disorders also occurred frequently (47%) and included inflammation, and reaction (i.e. bruise, itching, irritation) at the injection sites.

Fifty-seven percent of patients treated with peg-interferon experienced psychiatric adverse events, most commonly depression (29%) anxiety/emotional lability/irritability (28%), and insomnia (23%).

Nausea, anorexia, and diarrhea each occurred in around 20% of patients; weight loss occurred in 11% of patients. Alopecia occurred in 22% of patients (see Table 17).

Treatment Discontinuations and Dose Reductions for Adverse Events

Overall, 10% of patients in the PEG-Intron groups discontinued therapy due to adverse events compared to 6% in the INTRON A group. Fourteen percent of patients in the PEG-Intron groups required dose reduction compared to 6% in the INTRON A group. In many but not all cases, events resolved after stopping PEG-Intron therapy. Some patients continued to experience adverse events for several months after discontinuation of therapy.

Table 17. Most Common Adverse Events

Adverse Events	PEG-Intron 1.0 μg/kg	INTRON A $3X10^6$ U
	Percentage of Patients with Adverse Events	
Application Site Disorders		
Inject. Site Inflamm./Reaction	47	20
Body as a Whole		
Headache	56	52
Fatigue	52	54
Influenza-Like Symptoms	46	38
Rigors	23	19
Fever	22	12
Weight Decrease	11	13
Gastrointestinal System		
Nausea	26	20
Anorexia	20	17
Diarrhea	18	16
Abdominal pain	15	11
Musculoskeletal System		
Musculoskeletal Pain	56	58
Psychiatric Disorders		
Depression	29	25
Insomnia	23	23
Anxiety/Emot. lability/Irritabil.	28	34
Skin and Appendages		
Alopecia	22	22

Effect of Concomitant Medication on Reported Incidence of Adverse Events

During the study treatment period the use of drugs within the following classes increased compared to use at baseline. Use of analgesic/antipyretic, and anti-inflammatory agents (including NSAIDS) increased roughly 5-fold from 10% to 50%; use of antihistaminic drugs also rose five-fold from roughly 5 % to 25% and use of corticosteroids rose approximately 4-fold from 2% at baseline. Use of psychotherapeutic drugs including antidepressants, sedatives and hypnotics, and tranquilizers rose 3-4 fold; around 20-24% of patients received antidepressant drugs. The largest relative increase in drug use occurred for antimicrobial agents whose use increased from 1-2% at baseline to up to 14% during the treatment period.

The drugs were used as treatment or prophylaxis against the most common adverse events associated with interferons, namely flu-like symptoms, fever, headaches, myalgias, injection site reactions, depression, anxiety/irritability, and

insomnia. It is not clear to what extent the increased use of antimicrobial agents is due to interferon-induced symptoms and signs of inflammation.

There was no evidence of major differences in the use of concomitant drugs across treatment groups. Therefore concomitant drug use had no effect on the comparative safety profile. It is not clear what impact if any such use had on the incidence of reported adverse events.

Abnormal Laboratory Values

Neutrophils Neutrophil counts decreased in 70% of patients. Severe potentially life-threatening neutropenia ($<0.5 \times 10^9/L$) occurred in 1% of patients.

Platelets Platelet counts decreased in 20% of patients. Treatment with Peg-Intron resulted in severe decreases in platelet counts ($<50,000/mm^3$) in 1% of patients.

The incidence and severity of thrombocytopenia and neutropenia were greater in the two highest PEG-Intron groups compared to the interferon alfa group. Platelet and neutrophil counts on average reached a nadir by 4 weeks of interferon treatment and generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

Thyroid Function TSH abnormalities developed in 16% of patients and were associated with clinically apparent hypo-thyroidism (5%) or hyper-thyroidism (1%). Subjects developed new onset TSH abnormalities while on treatment and during the follow up period. At the end of the follow up period 7% of subjects still had abnormal TSH values.

Liver functions In 10% of patients treated with PEG-Intron ALT levels rose 2 to 5-fold above baseline. The elevations were transient and were not associated with deterioration of other liver functions. Mean ALT levels decreased to almost half of baseline values in all groups during treatment and then increased towards baseline in the post-treatment period.

Anti-interferon Antibodies

The development of binding antibody to interferon was about 10% in the peg-interferon groups and 15% in interferon group. Nine subjects developed low titer (<64) neutralizing antibodies. Three of the nine patients responded to treatment as shown in Table 18.

Table 18. Development of Neutralizing Antibody to Interferon alfa

Treatment Group	Patient Number	Serum Neutralizing Antibody Titer	Response to IFN Treatment
Peg-IFN 0.5 μg/kg	C24/062	6	NR
	C23/029	12	R
	C21/280	12	NR
Peg-IFN 1.0 μg/kg	C09/637	6	R
	I22/434	64	NR
PEG-IFN 1.5 μg/kg	C11/554	23	R
	I10/186	32	NR
IFN $3x10^6$ U	I09/130	5	NR
	C20/594	6	NR

NR = Non Responder
R = Responder

INTERFERON OVERDOSES

In the clinical study 13 patients accidentally received a dose greater than that prescribed. There were no instances in which a patient received more than 2.5 times the intended dose. The maximum dose received by any patient was 3.45 μg/kg weekly over a period of approximately 12 weeks. There were no serious reactions attributed to these overdoses

NARRATIVES OF SERIOUS ADVERSE EVENTS

Selected clinical summaries of serious adverse events are provided below. Deaths are listed first followed by other serious events grouped by organ system. The order in which the organ systems are listed is based on the clinical significance of the adverse events. Psychiatric adverse events were the most frequent and most clinically significant serious adverse events. The clinical manifestations of the most frequent serious adverse events appeared to be similar across treatment groups. The rarer adverse events did not appear to be specific to any treatment group. The clinical descriptions of these events were consistent with those of adverse events previously reported in the literature for interferon alfa and described in the drug label.

Deaths

Suicide: Patient 148 was a 42 year-old woman on PEG-IFN 0.5μg/kg for 25 weeks who died by self-inflicted gunshot wound. Of note is the lack of history of depression. No symptoms or signs of depression were noted by the patient's physicians.

Suicide, murder, paranoid reaction in the post-treatment period: Patient 598 was a 41 year-old man on IFN for 1 year and a history of depression, antisocial behavior, and drug abuse.

Sudden death associated with straining at stool: Patient 406 was a 59 year-old man on IFN for 21 weeks. Myocardial infarction was suspected as cause of death. There were neither history nor symptoms of cardiovascular disease and the study ECG was normal. No postmortem examination was performed.

Psychiatric Adverse Events

The narratives of the psychiatric adverse events indicate that suicidal behavior, namely ideation, attempt, or completed suicide, was commonly (but by no means invariably) associated with a previous history of depression or other psychiatric diagnoses. Depression and other psychiatric disorders occurred both during the interferon-treatment period and in the post-treatment period.

Abuse of illicit drugs or ethanol were reported. Very frequently drug abuse represented a relapse of drug addiction and was often associated with development of depression. Overdoses of illicit drugs were also reported. These events did not appear to be a manifestation of suicidal behavior.

Suicide attempt: Patient 057 was a 49 year-old woman who completed PEG-IFN 1.5 μg/kg for 1 year and attempted suicide (venisection and intake of 24 g of acetaminophen) in the post-treatment period. The patient had a history of depression and anxiety.

Suicide attempt, depression, addiction relapse: Patient 371 was a 33 year-old man who completed treatment with PEG-IFN 1.5 μg/kg. The suicide attempt occurred in the post-treatment period; depression and addiction relapse were also diagnosed at that time. There was a previous history of suicide attempt, depression, and drug abuse.

Suicidal gesture, depression, anxiety, agitation: Patient 053 was a 53 year old man on PEG-IFN 1 μg/kg for 1 year and a history of depression and drug abuse.

Suicidal ideation, depression, aggressive reaction: Patient 139 was a 40 year-old man on IFN-alfa-2b for 36 weeks and a history of depression.

Suicidal ideation, depression aggravated: Patient 824 was a 43 year-old woman on PEG-IFN 0.5 μg/kg for 1 year and a history of depression.

Suicidal ideation, depression, addiction relapse: Patient 96 was a 40 year-old woman on PEG-IFN 1.5 μg/kg for 8 weeks who became depressed with suicidal thoughts and resumed ethanol abuse. Patients had a history of suicidal attempts, depression and alcoholism.

Suicidal ideation, depression, aggressive moods: Patient 411 was a 29 year-old man, on PEG-IFN 1 μg/kg for 5 months. There was no previous history of depression.

Suicidal ideation, depression: Patient 012 was a 39 year-old man. PEG-IFN was discontinued after 42 weeks for severe depression and suicidal thoughts. There was no previous history of depression.

Suicidal ideation, depression: Patient 465 was a 33 year-old man; PEG-IFN 1.0μg/kg was discontinued after 8 months for severe depression and suicidal thoughts. There was no previous history of depression.

Suicidal ideation, emotional lability, depression: Patient 304 was a 34 year-old woman who was discontinued from PEG-IFN 0.5 μg/kg after about 10 months due to suicidal ideation. There was no previous history of depression.

Suicidal ideation: Patient 288 was a 39 year-old woman on PEG-IFN 1.5μg/kg and no previous history of depression. The event resolved with treatment and IFN was continued.

Depression: Patient 084 was a 37 year-old man on PEG-IFN 0.5 μg/kg for 9 months and a history of depression and drug abuse.

Addiction relapse/overdose: Patient 084 following discontinuation of PEG-IFN due to depression was hospitalized for respiratory failure and required assisted ventilation. A drug screen was positive for amphetamine, benzodiazepine, pentobarbital, marijuana and ethanol.

Depression, drug abuse: Patient 086 was a 34 year-old woman who completed PEG-IFN 1.5 μg/kg treatment. Depression developed and was followed by use of illicit drugs. The patient had a history of depression.

Depression, anxiety, addiction relapse: Patient 024 was a 28 year-old man on PEG-IFN 1.5 μg/kg for 2 months who became anxious, severely depressed an restarted IV drug abuse.

Depression: Patient 089 was a 59 year-old woman on IFN for 2 months who developed severe depression, fatigue and somnolence; previous history of depression.

Depression: Patient 638 was a 43 year-old man who completed one year of treatment with PEG-IFN 0.5 μg/kg. Depression began within 1 month of treatment and waxed and waned in severity. In the post-treatment period the patient was hospitalized for severe depression.

Addiction relapse/overdose, depression, agitation, hypothyroidism: Patient 517 was a 47 year-old man on PEG-IFN 0.5 μg/kg for 37 weeks. He became

depressed, agitated, irritable and overdosed on diazepam (#50 10 mg tabs), hydrocodone and dalmane. He developed hypothyroidism requiring treatment. There was a previous history of depression and drug abuse.

Substance abuse, Injury accidental: Patient 097 was a 47 year-old man who completed PEG-IFN 0.5 μg/kg treatment. The patient sustained a crush injury with pelvic and rib fractures and bladder injury. During hospitalization for the multiple trauma he developed ethanol withdrawal syndrome.

Addiction relapse: Patient 107 was a 31 year-old man on IFN for 11 months. The patient had history of drug abuse and depression and was hospitalized for detoxification from benzodiazepines.

Addiction relapse, overdose: Patient 306 was a 35 year-old man completed 1 year of treatment with PEG-IFN 0.5 μg/kg. He was hospitalized for an episode of loss of consciousness diagnosed as drug abuse and unintended overdose of lorazepam and valoron. There was a history of drug abuse.

Addiction relapse: Patient 297 a 35 year-old man discontinued IFN treatment after 6 months due to relapse of heroin abuse.

Cardiovascular Adverse Events

Myocardial infarction, septal, age undetermined, cardiomyopathy, severe depression of left ventricular systolic function: Patient 053 was a 53 year old man on PEG-IFN 1 μg/kg for 1 year. He became symptomatic and was diagnosed in the post IFN-treatment period.

Additional evidence of association of ischemic events with IFN consists of one case of myocardial infarction in study C97-058-01 (a PK study), two cases of retinal ischemia in the phase 3 study (see "Ophthalmic" narratives below), and post-marketing reports of ischemic colitis associated with interferon alfa-2b.

Renal Adverse Events

Nephrotic syndrome, interstitial nephritis: Patient 087 was a 42 year old man who completed 1 year's treatment with PEG-IFN 0.5 μg/kg. Dramatic increase in body weight and edema were first noted 1 month after the end of IFN treatment. At 3 months post-treatment heavy proteinuria (6g/24 hrs) was documented with normal urine microscopy, hematology and clinical chemistries. At 4 months post-treatment interstitial nephritis was diagnosed on renal biopsy (focal segmental glomerulosclerosis was included in the differential diagnosis) and corticosteroid treatment was begun for the nephrotic syndrome.

Hematologic Adverse Events

Autoimmune thrombocytopenia: Patient 0002 was a 58 year-old man who received PEG-IFN 1.0 μg/kg for 16 weeks. IFN was stopped when the platelet count dropped to 65×10^9 from 370×10^9 at baseline. Other hematology parameters including bone marrow aspirate were normal. Anti-platelet glycoprotein IIb/IIIa

was negative at baseline and elevated during treatment. Increased gingival bleeding was the only clinical manifestation of the cytopenia. Platelet count normalized on corticosteroid treatment. After several months of treatment corticosteroids were tapered off without recurrence of thrombocytopenia.

Autoimmune thrombocytopenia, epistaxis: Patient 157 was a 59 year-old woman who received PEG-IFN 1.0 μg/kg for 3 months. While on study, Parkinson's disease, gastritis, anxiety, and flu-like syndrome were diagnosed and were treated with biperiden, madopar, famotidine, acetaminophen, and a benzodiazepine. IFN was discontinued due to severe thrombocytopenia (27 $x10^9$). Anti-platelet glycoprotein Ia/IIa and ANA became weakly positive whereas they were negative at baseline. Bone marrow was not examined. Corticosteroid treatment was deemed unnecessary. Three months after discontinuation of IFN the platelet count was 102 $x10^9$.

Ophthalmic Adverse Events

Retinal ischemia, decreased visual acuity, cotton wool spots: Patient 021 was a 58 year-old man on IFN for 3 months. At 4 weeks of treatment he began to complain of decreased vision at night that progressively grew worse. There was no history of diabetes or cardiovascular disease. Ophthalmologic exam at 3 months showed cotton wool spots in the right eye and microvacular ischemia was documented by angiography. IFN was stopped and ophthalmologic changes were reported to be normal 8 weeks later.

Retinal vein thrombosis, vision disorder: Patient 361 was a 48 year-old woman on IFN for 7 months. Evaluation for scotomas in the right eye revealed a thrombosis of the upper temporal pole of the retinal vein with no involvement of the central vein.

Endocrine Adverse Events

Autoimmune thyroiditis ,myalgia, asthenia: Patient 049 was a 30 year-old man, on PEG-INF 1.5 μg/kg for 3 months. He developed asthenia, diarrhea, headaches, myalgia, low TSH, elevated T3 and T4 and positive anti-peroxidase antibodies. IFN was discontinued and carbimazole treatment was begun.

Infections

Because of the bone marrow suppressive effect of interferons alfa, serious infections were reviewed for unusual clinical manifestations or outcomes. The following events were described. Two cases of pneumonias presumed to be bacterial; one case of each of the following: appendicitis; peri-appendiceal abscess with peritonitis; retrouterine abscess in the presence of an IUD; oral abscess following dental extractions; labial abscess associated with controlled diabetes; tonsillitis presumed to be bacterial; erysipelas originating from a wound in the popliteal fossa; aseptic meningitis. The adverse events were not associated with clinically significant decreases in neutrophil counts and patients appeared to recover with treatment.

An unusual finding was the presence (in patient 206 on PEG-IFN 0.5 μg/kg) of necrotizing epithelioid granulomas in the post-treatment liver biopsy. A diagnosis of mycobacterium infection was considered but was not confirmed.

Neurologic Adverse Events

Left-sided facial paralysis associated with neutropenia and thrombocytopenia: Patient 022 was a 62 year-old man on PEG-IFN 1.0 μg/kg for 3 months. Bell's palsy developed while WBC was 0.81 $x10^9$ and the platelet count was 81 $x10^9$. Paralysis and cytopenias resolved after discontinuation of IFN.

Left-sided facial paralysis: Patient 347 was a 53 year-old woman on PEG-IFN 1μg/kg for two months and a history of diabetes. Severe Bell's palsy developed, IFN was stopped and corticosteroids begun; 15 weeks later mild facial drooping remained.

Oculomotor nerve paralysis, diplopia: Patient 577 was a 48 year-old man with insulin-controlled diabetes. IFN treatment was discontinued after 5 months because of double vision, and drooping left eyelid. Partial oculomotor nerve palsy was attributed to vasculitis caused by diabetes or IFN.

Hearing loss: Patient 068 was a 36 year-old woman who completed 1 year treatment with PEG-IFN 1.5 μg/kg. The patient complained of hearing loss and an audiogram showed a bilateral 30% loss of hearing (30 dB in the 1000 and 2000 Hz frequencies) that remained stable on continued IFN treatment.

Dermatologic Adverse Events

Psoriasis aggravated: Patient 149 was a 37 year-old woman on IFN for 3 weeks and a history of mild psoriasis controlled with topical coal extract. The patient developed a severe flare of psoriasis affecting the extremities and associated with arthralgias and eye irritation. IFN was stopped and cyclosporine and calcipotriene were required to control the psoriasis. Exacerbations of psoriasis recurred in the post-treatment period.

Generalized urticaria: Patient 318 was a 54 year-old woman on PEG-IFN 0.5 μg/kg who developed injection site erythema after the third dose. With the fourth dose the patient developed urticaria that began at the injection site and became generalized. IFN was discontinued and the patient was treated with corticosteroids.

Autoimmune Adverse Events

Systemic lupus erythematosus-like syndrome, Patient 327 was a 71 year-old woman who completed a 1 year course of PEG-IFN 1.5 μg/kg. Six weeks post-treatment the patient developed dyspnea, fever, and thoracic pain. Pericarditis with effusion and pleurisy were diagnosed and diclofenac was administered. GI bleeding occurred, was attributed to diclofenac and was treated with transfusion. A respiratory infection was treated with a cepahalosporin. Serologic testing was positive at high titer for ANA, DS-DNA, TPO, and for thyroid, spleen, thymus, and

smooth muscle. No treatment for the autoimmune disorder was considered necessary.

To the SLE case should be added the following autoimmune adverse events described above: aggravated psoriasis, thyroiditis, thrombocytopenia, and nephritis. In addition ulcerative colitis (presenting with fever, abdominal pain, and bloody diarrhea) has been associated with interferon alfa by postmarketing adverse event reports.

SUMMARY OF EFFICACY AND SAFETY

Efficacy of Peg-interferon alfa-2b

Primary Efficacy Outcome: Combined Virologic Response and ALT Normalization

- The response to 1.5 μg/kg peg-interferon alfa-2b treatment is superior to the response to treatment with $3X10^6$ U interferon alfa-2b.

- The response to 1.0 μg/kg peg-interferon alfa-2b treatment is superior to the response to treatment with interferon alfa-2b and is similar to the response to 1.5 μg/kg peg-interferon alfa-2b.

- The response to 0.5 μg/kg peg-interferon alfa-2b treatment is intermediate between the response to the two higher peg-interferon doses and the response to interferon alfa-2b.

- Long term studies are needed to determine [redacted]

- Studies are also needed to demonstrate that [redacted]

- HCV genotype 1 and levels of circulating HCV RNA > $2x10^6$ are significantly associated with less favorable response to treatment.

- Between 94 and 100% of responders have undetectable HCV RNA levels by 6 months of treatment. Discontinuation of peg-interferon treatment should be considered in patients who fail to clear HCV RNA by this time-point.

- Response rates were lower in African American and Hispanic patients and higher in Asian patients compared to Caucasian patients. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (9% of the total) was insufficient to allow meaningful conclusions about differences in response

rates after adjusting for prognostic factors. [redacted]

- A straight-forward numerical comparison across different clinical studies suggests that response rates to peg-interferon alfa-2b monotherapy are inferior to response rates to combination therapy with interferon alfa-2b plus ribavirin.

- [redacted]

- There is no information on treatment response in patients who have failed previous interferon alpha treatment.

Secondary efficacy outcomes

- Scores for liver inflammation/necrosis and liver fibrosis were not superior with peg-interferon alfa-2b treatment compared to interferon alfa-2b treatment.

- Time to response to treatment and time to relapse were not superior with peg-interferon alfa-2b treatment compared to interferon alfa-2b treatment.

- Health-Related Quality of Life Scores were not improved in any of the interferon treatment groups either during or after treatment.

Safety of Peg-interferon alfa-2b

Incidence of Adverse Events

- Patients receiving peg-interferon appeared to experience a greater number of adverse events (e.g. injection site reaction, fever, rigors, nausea) compared to patients receiving interferon.

- The number of adverse events in all body systems in general was higher in patients receiving the higher peg-interferon dosages.

- The types of adverse events were similar between peg-interferon and interferon groups.

Most Common Adverse Events

- Psychiatric adverse events occurred in 57% of patients treated with peg-interferon and depression was the most common (29%) of these events. Suicidal behavior (ideation, attempts, and suicides) occurred in 1% of all patients during or shortly after treatment with peg-interferon.

- Other common adverse events (reported by approximately 50% of patients) associated with PEG-Intron were "flu-like" symptoms, fever, fatigue, musculoskeletal pain, and application site disorders (i.e. bruise, itching, irritation).

Clinically Significant Adverse Events

- *Neuropsychiatric events:* Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior occurred in patients with and without a previous psychiatric disorder during peg-interferon treatment and follow-up. Peg-interferon should be used with extreme caution in patients with a history of psychiatric disorders. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. In severe cases, peg-interferon should be stopped immediately and psychiatric intervention instituted.

- *Bone marrow toxicity:* Peg-interferon suppressed bone marrow function, sometimes resulting in severe decreases in neutrophil or platelet counts.

- *Endocrine disorders:* Peg-interferon caused or aggravated hypothyroidism and hyperthyroidism.

- *Cardiovascular events:* Arrhythmia, cardiomyopathy and myocardial infarction were observed in patients treated with Peg-interferon. Peg-interferon should be used cautiously in patients with cardiovascular disease. Patients with a history of myocardial infarction and arrhythmic disorder should be closely monitored.

- *Autoimmune disorders*: Development or exacerbation of autoimmune disorders (e.g. thyroiditis, thrombocytopenia, rheumatoid arthritis, interstitial nephritis, systemic lupus) was observed. Peg-interferon should be used with caution in patients with autoimmune disorders.

- *Ophthalmologic disorders*: Cotton wool spots and retinal vein obstruction have been observed after treatment with peg-interferon or interferon.

Precautions

- *Patients with renal failure*: Patients with impairment of renal function should be closely monitored for signs and symptoms of interferon toxicity and doses of peg-interferon should be adjusted accordingly. Peg-interferon should be used with caution in patients with creatinine clearance <50 ml/min.

- *Geriatric Patients*: There were insufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Typical adverse reactions to interferons might be more severe in the elderly, therefore caution should be exercised in use of peg-interferon in this population.

- *Immunogenicity*: One percent of patients receiving peg-interferon developed low-titer neutralizing antibodies to interferon. The clinical and pathological significance of the appearance of serum neutralizing antibodies is unknown.

- *Patient monitoring:* Patients were monitored with periodic clinical and laboratory evaluations per protocol and as necessary and interferon dose reduction or discontinuation for adverse events were necessary. In many but not all cases adverse events resolved after stopping peg-interferon treatment

- *Laboratory tests:* Patients on peg-interferon therapy should have hematology and blood chemistry testing before the start of treatment and then periodically thereafter. In the clinical trial CBC (including neutrophil and platelet counts) and chemistries (including AST, ALT and bilirubin) were measured during the treatment period at weeks 2, 4, 8, 12, and then at 6-week intervals or more frequently if abnormalities developed. TSH levels were measured every 12 weeks during the treatment period.

CONCLUSIONS

In patients with compensated HCV hepatitis response rates to peg-interferon alfa-2b 1.5 μg/kg and 1.0 μg/kg (once weekly SC for 48 weeks) are similar to each other and are superior to response rates to interferon alfa-2b monotherapy ($3x10^6$ U three times weekly SC for 48 weeks). The number of adverse events in the two highest peg-interferon dose groups is generally higher than the number in the interferon group and tends to be highest in the 1.5 μg/kg dose group. The 1.0 μg/kg dose of peg-interferon alfa-2b appears to have the most favorable risk/benefit profile of the doses tested.

Peg-interferon alfa-2b and interferon alfa-2b cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients with persistently severe or worsening signs or symptoms of these conditions need to be withdrawn from therapy. In many but not all cases these disorders resolve after stopping peg-interferon therapy.

Patients should be advised that periodic clinical and laboratory evaluations are necessary. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians

Chronic HCV hepatitis is a life-threatening disease. It is estimated that after 2-3 decades of HCV infection, 20% of patients may develop cirrhosis and about 1-2% of patients may develop hepatocellular carcinoma. Chronic hepatitis C results in an estimated 8,000 to 10,000 deaths each year.

Given the serious complications associated with untreated chronic hepatitis C, and the response to peg-interferon treatment (loss of HCV RNA detection and

ALT normalization in 24% of treated patients), the risks of peg-interferon treatment are judged to be acceptable.

It should be noted that response rates to peg-interferon alfa-2b monotherapy appear to be inferior to those of combination therapy with interferon alfa-2b plus ribavirin.

RECOMMENDED REGULATORY ACTION

PEG-Intron, peg-interferon alfa-2b has been shown to be safe and effective for the treatment of compensated chronic hepatitis C in patients not previously treated with interferon alpha who have compensated liver disease and are at least 18 years of age. Therefore, approval of the marketing application by Schering Plough is recommended.

1/25/01

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