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**MEMORANDUM**

**FROM**

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*LM*

**THROUGH**

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**TO**

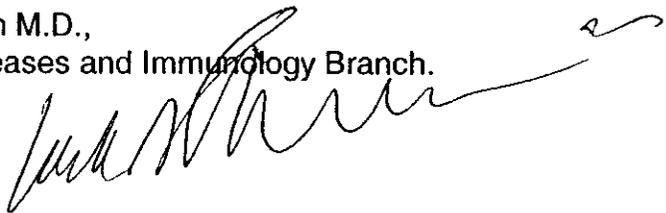
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*KW*

**TOPIC**

Clinical Review  
Biologic License Application Supplement  
BL 103949/BLA 99-1488  
PEG-Intron™ (Peginterferon alfa-2b) SCH 54031/ REBETOL®  
(Ribavirin) SCH 18908

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*K.W.* 11-4-01

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## INTRODUCTION

### Filing of application

On February 5, 2001, Schering Corporation submitted a Biologics License Application Supplement (BL 103949/ BLA 99-1488) for PEG-Intron™ (peginterferon alfa-2b, SCH 54031) and REBETOL™ (ribavirin, USP; SCH 18908) combination therapy for the treatment of chronic hepatitis C.

### Study products

CMC data are cross-referenced to other license applications. Peg-interferon alfa-2b is manufactured by conjugation of interferon alfa-2b with a 12-KD monomethoxy polyethylene glycol molecule. The clearance of peginterferon alpha is longer than that of interferon allowing once weekly dosing and increased drug exposure compared to interferon alpha.

Ribavirin is a guanosine analogue that has *in vitro* antiviral activity against a number of different RNA viruses. Ribavirin enters the red blood cell and has an intracellular half-life of approximately 300 days. Ribavirin monotherapy is not efficacious in chronic HCV infection. Aerosolized ribavirin was licensed in 1988 for the treatment of respiratory syncytial virus in infants.

Peginterferon alfa-2b was supplied to study subjects as a lyophilized powder (50 and 150 µg/vial) and interferon alfa-2b was supplied as a solution (3x 10<sup>6</sup> U/vial). Both drug products were packaged in single dose, rubber-stoppered vials. Peginterferon powder was reconstituted using the vial of sterile water provided. Ribavirin was supplied as 200 mg capsules packaged in a bottle containing 180 capsules.

### Chronic hepatitis C

Hepatitis C virus (HCV) is an enveloped RNA virus in the Flaviviridae family. Six viral genotypes and 30 subtypes are known. HCV is transmitted primarily by the parenteral route.

HCV causes 20% of all cases of acute viral hepatitis and 70-90% of all cases of chronic viral hepatitis. The acute infection is asymptomatic in the majority of cases; only one third or less of all affected patients develops fatigue, malaise, weakness, nausea, or anorexia, and/or icterus. Fulminant liver failure occurs very rarely. Within 1-3 weeks of infection, HCV-RNA is detectable in the circulation. By 2 months serum alanine transferase (ALT) is elevated in nearly all cases. By 3 months anti-HCV antibodies are detectable in 90% of cases. Spontaneous recovery from infection occurs in 15% of cases. Patients with chronic HCV infection have persistent viremia and in most cases abnormal ALT levels.

In the US around 50% of children and 85% of adults infected with HCV develop chronic hepatitis; approximately 4 million persons are chronically infected with HCV. After decades, liver cirrhosis develops in about 20% of adults with chronic

HCV infection. In children with chronic HCV the incidence of cirrhosis is lower compared to adults due to shorter duration of infection and possibly slower rate of progression of disease. The development of cirrhosis is associated with liver failure, with portal hypertension and their related complications, and with the development of hepatocellular carcinoma. Chronic HCV infection causes 12,000 deaths per year and is the primary cause for liver transplantation in the US.

Chronic HCV infection is also associated with autoimmune thyroiditis, membranoproliferative glomerulonephritis, cryoglobulinemia, seronegative arthritis, pulmonary fibrosis, polyarteritis nodosa, and aplastic anemia.

Genotype 1 is the most common (70%) HCV genotype and is less likely to respond to treatment compared to HCV genotypes 2 and 3. High circulating HCV load, defined as  $>2 \times 10^6$  RNA copies/ml serum, and presence of liver cirrhosis are two other indicators of unfavorable response to treatment.

#### Treatment of chronic hepatitis C

Alpha interferons were the first antiviral agents to be licensed for the treatment of patients with chronic hepatitis C. Alpha interferons induce loss of detection of circulating HCV RNA, normalization of serum transaminase levels, and modest reduction in liver inflammation. Different dose regimens (including dose escalation and dose de-escalation), and duration of treatment (generally 6 and 12 months of chronic dosing) have been studied. The result of most studies of monotherapy was that 6 months after the end of treatment  $< 20\%$  of patients had undetectable HCV RNA.

Strategies to improve response rates involve combination therapy and use of interferons with a longer half-life.

Combination treatment with alpha interferon and ribavirin roughly doubles (to around 40%) the proportion of responders and is the most efficacious therapy currently available for chronic hepatitis C.

Peginterferon alfa-2b was licensed on January 19, 2001 based on a phase 3 trial in which peginterferon monotherapy was compared to Intron-A monotherapy. The proportion of patients with loss of HCV RNA was 24% for the peginterferon group and 12% in the interferon alfa group. Although peginterferon was more efficacious than interferon alfa-2b, the incidence and severity of peginterferon alfa-2b -induced toxicity was higher than the toxicity induced by interferon alfa-2b. Peginterferon alfa-2b was not directly compared to combination therapy with Intron-A and ribavirin, but the magnitude of the viral response to peginterferon suggests that it is likely to be less effective than combination therapy with interferon alpha and ribavirin. Peginterferon monotherapy appears to be a treatment option for patients who are intolerant or wish to avoid the additional risks associated with ribavirin treatment. Candidates for monotherapy would include for example patients with hemolytic anemias such as sickle cell anemia and thalassemia major.

Factors that affect response rates include viral genotype (genotype 1 is associated with lower response rates) and viral load, with HCV RNA of  $2 \times 10^6$ /ml serum generally used as the cut point. In addition, loss of viral RNA in the initial months of treatment is a predictor for sustained viral response. Treatment discontinuation should be considered in patients who still have detectable viral RNA by week 12-24 of treatment. Long-term studies of lower doses of peginterferon monotherapy are underway in patients who fail to clear virus to determine if such treatment reduces progression of fibrosis and cirrhosis and the serious complications of cirrhosis. However, even among patients who have a sustained response to treatment, it is not known if loss of detection of HCV RNA six months after the end of treatment will halt the progression of liver disease to cirrhosis and its associated complications including hepatocellular carcinoma.

Alpha interferons adversely affect a number of organ systems. Flu like symptoms are very common, as are gastrointestinal disturbances. Bone marrow toxicity with decrease in platelet and neutrophil counts is common. Severe cytopenias including aplastic anemia occur but are less frequent. Neuropsychiatric disorders occur in many patients receiving alpha interferons. Manifestations include severe depression, suicidal ideation and suicide, emotional lability, aggressive behavior, and addiction relapse.

Interferon alpha may induce or aggravate autoimmune disorders, ischemic disorders, and can adversely affect certain host defenses and contribute to the development of serious infections. Interferons are abortifacients.

Patients who take interferons should be monitored for toxicities, and dose-modification or discontinuation instituted as necessary. Serious adverse events frequently but not always reverse with discontinuation of treatment. Regular clinical and laboratory assessment of patients and patient education are essential for safety.

Toxic effects of ribavirin include hemolysis, teratogenicity, embryocidal activity, and mutagenesis. The main dose-limiting toxicity of ribavirin is hemolytic anemia, which may induce ischemic cardiac or neurologic events. The anemia is usually reversible once treatment is discontinued.

#### **ADMINISTRATIVE ISSUES AND DATA AUDITS**

Please see **APPENDIX 1**.

#### **ONGOING CLINICAL STUDIES**

For text and **Tables 1-2**, please see **APPENDIX 2**.

#### **LISTING OF CLINICAL STUDIES**

**Table 3** lists the clinical studies that support this license application.

**Table 3. Studies of Peginterferon  $\alpha$ -2b plus Ribavirin in Patients with Chronic Hepatitis C**

Study No. Subject No.	Study Design	Study Drug Doses
I96-403 N= 72	Phase 1, open-label, active-control, parallel group, multiple-dose, study.	Peginterferon $\alpha$ -2b (0.35-1.4 $\mu$ g/kg SC QW) plus Ribavirin (600-1000/1200 mg PO) for 24 weeks
C/I98-580 N= 1530	Phase 3 multicenter, randomized, open-label, active-control, parallel group study with 48 weeks of treatment and 24 weeks of follow-up.	Peginterferon $\alpha$ -2b (1.5 $\mu$ g/kg SC QW) plus Ribavirin (800 mg/day PO).  Peginterferon $\alpha$ -2b (1.5 $\mu$ g/kg SC QW for 4WK then 0.5 $\mu$ g/kg for 44 WK) plus Ribavirin (1000-1200 mg/day PO).  Interferon $\alpha$ -2b A 3x10 <sup>6</sup> U SC TIW plus Ribavirin 1000-1200 mg/day PO.

The sponsor's personnel audited both studies and reviewed original patient records to evaluate the accuracy of the case report forms.

A data safety review board reviewed the safety data of the phase 3 study. The board met three times during the course of the study and also met at the start and end of the study. The board did not recommend changes to the conduct of the study.

Subjects eligible to enroll in the phase 3 study were identified through a screening protocol (Protocol [ ] ). Approximately 1850 subjects would be screened at approximately 70 study sites to enroll approximately 1,575 subjects (525 per treatment arm). The maximum number of subjects per site would be 100 (6% of the total).

### **PROTOCOL C/I98-580**

#### **OBJECTIVES, HYPOTHESES, DOSE SELECTION**

The phase 3 study was a single multinational study run under two designations, C98-580 for US sites, and I98-580 for international sites. Data from all study sites were combined for a single analysis. The randomization period for the study was from January 1999 to May 1999. The study was completed on October 6, 2000.

#### Study title

"Comparison of peginterferon alfa-2b (PEG-Intron, SCH 54031) plus REBETOL (SCH 18908) vs. Interferon alfa-2b (INTRON A, SCH 30500) plus REBETOL for treatment of chronic hepatitis C in previously untreated adult subjects."

#### Study objectives

To evaluate the safety and efficacy of two peginterferon plus ribavirin regimens compared to interferon plus ribavirin.

#### Rationale for dose selection

At the time the present study was designed the sponsor used the following data to select the doses to be studied.

1. Peginterferon:

A dose ranging study (Protocol C/I 97-010) of peginterferon monotherapy (0.5, 1, or 1.5 µg/kg SC once weekly) versus interferon monotherapy (3 x 10<sup>6</sup> U SC three times weekly) in patients with chronic HCV hepatitis was ongoing. As shown in the table below an analysis of antiviral activity after 6 months of treatment showed that the proportion of patients with undetectable HCV-RNA was numerically higher in all three peginterferon groups. The proportion of responders was highest in the 1.5 µg/kg dose group (see Table 4).

**Table 4. Antiviral Activity (HCV RNA <2,000 copies/ml) at 24 Weeks of Treatment**

Treatment Groups <sup>1</sup>			
PEG 0.5 µg/kg N=315	PEG 1.0 µg/kg N=297	PEG 1.5 µg/kg N=304	IFN 3 x 10 <sup>6</sup> U N=303
42%	48%	57%	32%

<sup>1</sup>Protocol C/I97-010

The degree of anti-viral activity achieved with peginterferon alfa-2b alone suggested that treatment with peginterferon alfa-2b and ribavirin might be more efficacious compared to treatment with interferon alfa-2b plus ribavirin. The results also suggested that the 1.5 µg/kg was superior to the 1.0 µg/kg dose.

*Reviewer's comments*

*The sponsor recognized the possibility that additional virologic responses might occur by the end of the 48- week treatment period (admittedly only very few, ≤5%, had been seen with previous treatment regimens). The sponsor also recognized that in the post-treatment period a sizable proportion of patients who responded would relapse (as many as 50% of patients who respond to IFN monotherapy relapse). However the sponsor believed that based on his analyses of the IFN and IFN/R database he could reliably predict the rates of sustained response from in-treatment responses in study C/I 97-010. This hypothesis led to the choice of the low and high doses of peginterferon (0.5 and 1.5 µg/kg) to be tested in the present study.*

*Unfortunately, after study C/I 97-010 was completed the data showed that the efficacy of the peginterferon 1.5 µg/kg dose was not superior to that of the peginterferon 1.0 µg/kg dose (23% response vs. 24%) due to higher relapse in the peginterferon 1.5 µg/kg group. The incidence of adverse events was numerically somewhat higher in the peg 1.5 dose group compared to the peg 1.0 dose group; the two most notable examples were weight loss (21% vs. 11%) and alopecia (34% vs. 22%). As a result of more*

*favorable risk benefit the agency licensed the peginterferon 1.0 µg/kg dose for monotherapy of HCV.*

The sponsor also hypothesized that an induction treatment with peginterferon 1.5 µg/kg for 4 weeks would boost the response to treatment in the PEG 0.5/R arm. The rationale was based on sponsor's analyses of interferon alpha data that apparently suggested that time to viral response was shorter with higher doses of interferon.

*Reviewer's comment*

*Time to viral response was a secondary efficacy endpoint in study C/I 97-010. In the peginterferon groups, despite several-fold increases in drug exposure, time to viral response was not shorter compared to time to response in the interferon group. These results did not support the sponsor's hypothesis about the utility of the induction treatment.*

2. Peginterferon and ribavirin:

A phase 1 study (protocol I96-4030) evaluated the following peginterferon plus ribavirin combination treatments in 72 patients with chronic hepatitis C infection:

- Peginterferon 0.35 µg/kg/week plus ribavirin 600 or 800 mg/day
- Peginterferon 0.7 µg/kg/week plus ribavirin 600, 800, or 1000-1200 mg/day
- Peginterferon 1.4 µg/kg/week plus ribavirin 600, 800, or 1000-1200 mg/day

Preliminary analyses of antiviral activity at 12 weeks of treatment suggested the presence of an interaction between ribavirin and peginterferon dosages based on the following observations. The peginterferon 0.35 µg/kg dose appeared to have antiviral activity only when combined with ribavirin 800 mg. The peginterferon 0.7 µg/kg dose appeared to be most active when combined with ribavirin 1000-1200 mg. The peginterferon 1.4 µg/kg dose appeared to be equally active with the three ribavirin doses tested.

*Reviewer's comment*

*A report of this study is not included in the BLA supplement. The clinical reviewer has not reviewed the study. It is not clear if PK data were obtained in addition to the PD data. The Peg doses (0.5 and 1.5 µg/kg) used in the major efficacy study were not evaluated in study 4030. Selection of ribavirin dose for the present phase 3 study was based on in-treatment response data.*

Based on the preliminary results of the two studies discussed above, the sponsor hypothesized that peginterferon 1.5 µg/kg once weekly plus ribavirin 800 mg daily would be superior in efficacy and would have a more favorable safety profile than the licensed regimen of Interferon 3x10<sup>6</sup> Units thrice weekly plus ribavirin 1000-1200 mg daily. The sponsor also hypothesized that peginterferon 0.5 µg/kg once

weekly plus ribavirin 1000-1200 mg daily would be equivalent in efficacy and would have a more favorable safety profile than the IFN/R. The final hypothesis was that an induction treatment with peginterferon 1.5 µg/kg once weekly for 4 weeks would boost the response to treatment in the PEG 0.5/R arm.

*Reviewer's comment*

*The selection of the peginterferon and ribavirin doses to be tested in the efficacy study (C/I98-580) was based on preliminary in-treatment data, and on an underpowered dose-ranging study .*

**MAJOR PROTOCOL AMENDMENTS (C/I 98-580)**

The original study protocol is dated December 4, 1998. The study began on February 1, 1999, and ended on October 6, 2000.

Data analysis plan

The statistical analysis plan was revised on December 11, 1998, January 4, 2000 and May 25, 2000 (see description in the Clinical Trial Outline section).

Change in administration of ribavirin

An amendment dated 07/13/99 stressed the requirement to take ribavirin with food. This recommendation was based on results of PK/PD studies that showed an increase in ribavirin absorption in the presence of food.

*Implementation of change in REBETOL administration in study C/I98-580:  
The sponsor provided the following additional information.*

- *All investigators and IRBs were informed of the change in administration of REBETOL*
- *At the time the change was instituted approximately 150 patients had been entered in the study and had begun treatment.*
- *Study patients were instructed to take the two daily doses of REBETOL one with breakfast and the other with dinner.*

*Documentation of study drug dosage and administration in study C/I98-580: Patients kept a daily medication diary. The diary was not modified after the change in ribavirin administration was begun. For interferon or peginterferon patients entered the dose taken and circled a number (1-6) denoting the injection site. The diary contains two columns with the headings "# Ribavirin Caps AM" and "# Ribavirin Caps PM". The patients were instructed to circle each day a number (0-3) denoting the number of capsules taken. Therefore the diary does not document how ribavirin was taken with respect to food. The case report form does not capture additional information on ribavirin administration.*

*Assessment:*

*The agency has previously determined that there is a marked effect of food on the absorption of ribavirin. In the present study approximately 90% of*

*patients took the entire course of ribavirin with food. The few patients already on study at the time the change in ribavirin administration occurred took ribavirin with food for  $\geq 50\%$  of their treatment course.*

*Additional studies may be needed to confirm and characterize the effects of food on single-dose ribavirin absorption (e.g. effects of high fat vs. high non-fat caloric intake) and achievement of steady state after multiple dosing of ribavirin.*

#### Requirement for use of contraceptive

The amendment dated 07/13/99 also stressed the need for adequate contraceptive use by all study subjects and their partners.

### **CLINICAL TRIAL OUTLINE (C/I 98-580)**

#### Study design

Multi-center, randomized, open-label, active-controlled (INTRON A/REBETOL), parallel group, phase 3 study of two PEG-Intron/REBETOL regimens in approximately 1500 subjects with chronic hepatitis C. Subjects were randomly assigned to three treatment arms (1:1:1) with stratification based on HCV genotype (1 vs. non-1) and presence of liver cirrhosis. Subjects were treated for 48 weeks and were followed up for 24 weeks post-treatment.

A central laboratory performed all baseline genotype testing. At each study site a local pathologist made the diagnosis of presence/absence of cirrhosis using protocol criteria developed by the central assessor ( [ ] pathologist). The local pathologist's diagnosis was used for the purpose of stratification. The presence or absence of cirrhosis at baseline was also determined in a blinded fashion by the ( [ ] pathologist. His diagnosis was used for the purpose of the covariate adjustment used in the primary efficacy analysis. (See Statistical Analysis section).

The sponsor estimated that approximately 1800 patients would be screened to meet the target enrollment. The maximum number of subjects enrolled per site would be 100.

#### Randomization

Study sites requested number assignment and randomization from the sponsor who forwarded the request to the Central Randomization Center. The Central Randomization Center informed the study site of the subject number and treatment allocation.

#### Dosing

The comparator arm was treated with REBETRON using the labeled dosing regimen of interferon alfa-2b  $3 \times 10^6$  Units administered subcutaneously three times weekly together with ribavirin 1000-1200 mg/day administered orally for 48 weeks.

The experimental treatment groups received one of the following two regimens:

1. Peginterferon 0.5 µg/kg SC once weekly plus ribavirin 1000/1200 mg/day orally for 44 weeks. This regimen was preceded by a 4-week induction period with peginterferon 1.5 µg/kg/week plus ribavirin 1000/1200 mg/day. The induction treatment was used in the belief that it would induce more rapid loss of HCV-RNA.
2. Peginterferon 1.5 µg/kg SC once weekly plus ribavirin 800 mg/day orally for 48 weeks. The 800 mg dose of ribavirin was intended to minimize the risk of additive/synergistic hematologic toxicity of interferon and ribavirin.

In this review the following short-hand designations will be used for the three dose regimens.

Peginterferon $\alpha$ -2b 1.5 µg/kg plus ribavirin:	PEG 1.5/R
Peginterferon $\alpha$ -2b1.5 then 0.5 µg/kg plus ribavirin:	PEG 0.5/R
Interferon $\alpha$ -2b $3 \times 10^6$ U plus ribavirin:	I/R.

Ribavirin is available only as 200 mg capsules and was taken orally in 2 divided doses, morning and evening. Subjects in the 1000/1200 mg/day ribavirin dose group weighing <75 kg received 1000 mg daily as two 200 mg capsules in the morning and three 200 mg capsules in the evening. Subjects >75 kg received 1200 mg daily as three 200 mg capsules morning and evening. Subjects who were treated with 800 mg/day of REBETOL received two 200 mg capsules in the morning and two 200 mg capsules in the evening. Subjects were instructed to take their REBETOL with food, as this increases availability.

#### Dosing compliance

Patient compliance with study treatments was monitored by counting medication vials that patients returned, by reviewing entries in a diary that the patients were required to maintain, and by questioning subjects about injection dates. From this information the compliance of each patient was assessed and recorded in a study treatment ledger. For the purpose of data analyses subjects were judged to be compliant if they had received  $\geq 80\%$  of doses as assigned including doses modified as required by the protocol.

#### Dose modification rules

Patients who reduced their ribavirin dose because of adverse events continued on the same reduced dose of ribavirin (600 mg daily divided as 200 mg in am and 400 mg in pm) even after the adverse event resolved.

Patients who reduced their dose of peginterferon or interferon (doses were halved in all treatment groups) because of adverse events resumed full dosing when the adverse event resolved. If the adverse event recurred the subject could return to the previously tolerated lower dose level for the remainder of the study. Alternatively the subject could permanently discontinue treatment.

Patients who interrupted treatment for longer than two weeks terminated treatment permanently and entered the follow up period.

Subjects were to be withdrawn from study treatment for the following reasons: Serious or life-threatening (grade 4) adverse event, pregnancy, subject's or investigator's choice, non-compliance, failure to disclose history of suicide ideation or attempt.

The following rules (Table 5) were used for abnormal hemoglobin, neutrophil and platelet counts, bilirubin, creatinine, and transaminase levels

**Table 5. Rules for Dose Reduction<sup>1</sup>**

	Dose Reduction (see Table 2)	Permanent Discontinuation of Treatment (IFN, PEG, PEG Induction and Ribavirin)
Hemoglobin	<10 g/dL (ribavirin) <sup>a</sup>	<8.5 g/dL
	Cardiac Subjects only: $\geq 2$ g/dL decrease during any 4 week period during treatment (both study medications) <sup>a</sup>	Cardiac Subjects only: <12 g/dL after 4 weeks of dose reduction
White blood count	$<1.5 \times 10^9$ (IFN, PEG and PEG induction) <sup>a</sup>	$<1.0 \times 10^9/L$
Neutrophil count	$<0.75 \times 10^9/L$ (IFN, PEG and PEG induction) <sup>a</sup>	$<0.5 \times 10^9/L$
Platelet count	$<80 \times 10^9/L$ (IFN, PEG and PEG induction) <sup>a</sup>	$<50 \times 10^9/L$
Bilirubin - Direct		2.5 x upper limit of normal
Bilirubin - Indirect	$>5$ mg/dL ( $>85.5 \mu\text{mol/L}$ ) <sup>b</sup> (ribavirin) <sup>a</sup>	$>4$ mg/dL ( $>68.4 \mu\text{mol/L}$ ) (for $>4$ weeks)
Creatinine		$>2.0$ mg/dL ( $>176.8 \mu\text{mol/L}$ )
ALT/AST		2x Baseline and $>10$ x upper limit of normal

<sup>1</sup>from protocol C198-580

Best Possible Copy

Subjects who develop mild depression would be evaluated weekly (by visit or by phone) for 4-8 weeks. If depression remained stable the subject could resume protocol monthly visits with instructions to call the investigator immediately as necessary.

Subjects with moderate depression would have their dose of interferon reduced in half and be assessed weekly (by visit or phone, at least two visits should be in office) for 4-8 weeks. These subjects could remain on reduced interferon dosing if stable. If the subject's symptoms did not improve but were stable for 4 weeks psychiatric consultation would be considered. If subject's condition worsened, antiviral treatment would be stopped and appropriate psychotherapeutic management would be instituted including weekly or biweekly evaluation until status returned to baseline. Subjects with severe depression or suicidal ideation/attempt would discontinue all study medications and would receive psychiatric treatment.

Inclusion criteria

Study subjects had to meet the following criteria.

- Adult men and women 18-70 years of age. Subjects  $> 65$  years must be in good health.
- Serum positive for HCV-RNA by quantitative PCR assay.

- Elevated ALT.
- Liver biopsy within 12 months with diagnosis of chronic hepatitis.
- Compensated liver disease.
- Hematologic, biochemical, and serologic criteria:
  - Hgb >12 g/dL in women, >13 g/dL in men.
  - WBC >3,000/mm<sup>3</sup>, ANC >1,500/mm<sup>3</sup>
  - Platelets >100,000/mm<sup>3</sup>
  - Direct and indirect bilirubin, albumin, TSH, serum creatinine, WNL.
  - ANA<1:160; HIV and HBsAg negative.
  - Alpha fetoprotein WNL, or if ≤50 ng/ml a negative abdominal ultrasound
  - Serum pregnancy test negative.
- Women practicing adequate contraception (namely IUD, oral contraceptives, progesterone implants, surgical sterilization, barrier method [diaphragm + spermicide], or monogamous relationship with a man who had a vasectomy or is using a condom with spermicide) during and for six months after the end of treatment.
- Men practicing adequate contraception (vasectomy, use of a condom and spermicide, monogamous relationship with a woman who practices an acceptable method of contraception) during and for six months after the end of treatment

#### Exclusion criteria

Subjects were to be excluded from enrollment into the study for the following reasons.

- Previous treatment ever with any interferon; treatment with any other antiviral or immunomodulatory agent within 2 years.
- Hypersensitivity to interferon, peginterferon or ribavirin.
- Any other cause for liver disease other than chronic HCV.
- Hemophilia or any other condition that would prevent a liver biopsy.
- Hemoglobinopathies, advanced liver disease, organ transplants.
- Preexisting medical condition such as:
  - Preexisting severe psychiatric illness, especially severe depression, psychosis.
  - CNS trauma or active seizure disorder.
  - Significant cardiovascular dysfunction including abnormal ECG.
  - Poorly controlled diabetes mellitus.
  - Chronic pulmonary disease.
  - Immunologically mediated disease.
  - Condition requiring chronic systemic administration of steroids.
  - Clinical gout.
  - Substance abuse.
  - Clinically significant retinal abnormalities.

#### Efficacy outcomes

Primary:

The primary efficacy outcome was loss of detectable serum HCV-RNA. Serum HCV-RNA testing was performed by quantitative polymerase chain reaction at a

central laboratory [1]. A subject was classified as a responder if the subject was HCV-RNA negative at 24 weeks post-treatment. All other subjects, including those who discontinued before the final HCV-RNA evaluations were obtained, were considered non-responders.

Secondary:

The following were the principal secondary endpoints listed in order of importance.

1. Normalization of ALT at 24 wks post-treatment.
2. Loss of HCV-RNA detection at the end of treatment.
3. Normalization of ALT at the end of treatment.
4. Improvement from baseline in biopsy scores (Knodell and Metavir) at 24 wks post-treatment.

Both Knodell and Metavir are composed of various categories that are combined to yield two final indices. One index is for liver necrosis and inflammation, and the other index is for liver fibrosis. A single assessor (liver pathologist at AFIP) scored the study's liver biopsies in a blinded fashion.

The Knodell Histologic Activity Index for inflammation contains the following components.

- I: periportal bridging necrosis (scores 0-10)
- II: intralobular degeneration and necrosis (scores 0-4)
- III: portal inflammation (scores 0-4)

The combined post-treatment index HAI: I+II+III (scores 0-18) was compared to the pre-treatment index and was categorized as follows.

- Improved: post-treatment index  $\leq 2$  units.
- Unchanged: post-treatment index within  $\pm 1$  unit.
- Worsened: post-treatment index  $\geq 2$  units.

The post-treatment Knodell Histologic Activity Index for Fibrosis (HAI: IV, scores 0-4) was compared to pre-treatment and was categorized as follows.

- Improved: post-treatment index  $\leq 1$  unit.
- Unchanged: post- and pre-treatment indices are the same.
- Worsened: post-treatment index  $\geq 1$  unit.

*Reviewer's comment*

*The changes in the qualitative scores that define improvement in liver biopsy are very small. It is not clear how clinically meaningful such changes are.*

#### Definition of protocol time points

The treatment period was defined as start date to stop date +7days. Time windows for each time point were prospectively defined. The window for the end of treatment (week 48) was days 309 to 364. The window for follow-up week 24 (the time point for assessment of the primary efficacy outcome) was follow up days 141

to 196. When multiple values were available within a time window, the worst value in the window was assigned to that time point.

#### Clinical and laboratory evaluations

One certified laboratory performed all hematology and chemistry measurements at two central sites (one in US the other in Europe). Local laboratories could be used for repeat testing requiring for safety assessments.

Health Related Quality of Life (HQL) was evaluated using the SF-36 scale with additional generic scales and hepatitis C specific scales. HQL data were collected at baseline, at week 12, 24, 36 and 48 during treatment and at week 12 and 24 of the post-treatment period. In addition, the mental health and vitality domains were collected (using an abbreviated HQL form) at treatment week 2, 4, 6, 8, 18, 30, and 42.

Serum samples were collected at treatment weeks 12, 24, and 48 to perform population pharmacokinetic analyses for PEG-Intron and for REBETOL. Serum samples were also collected at entry for the PEG-Intron PK analysis.

#### Statistical analyses

##### Sample Size Calculations

A study with 525 patients per treatment group would have 90% power ( $\alpha=5\%$  two-sided) to detect a non-inferiority margin of 10% for peginterferon ribavirin treatment.

##### Primary Efficacy Analysis

Treatment responses (loss of detection of HCV-RNA at 6 months after the end of treatment) would be analyzed using a logistic regression model with main effects due to treatment, genotype (type1 vs. all others), and presence of cirrhosis. Viral genotype and presence of cirrhosis were two stratification variables.

##### *Reviewer's comment*

*The original protocol did not specify time to reach endpoint and did not contain the statistical hypothesis of the study. The sponsor proposed a non-inferiority study, using a margin of 10%. That is, that the lower bound of the 95% confidence interval for the treatment difference had to exclude an absolute difference of 10% worse with peginterferon and ribavirin. The agency and the sponsor did not reach agreement on the criteria necessary for establishing non-inferiority between treatment response in patients receiving interferon and ribavirin and patients receiving peginterferon 1.5  $\mu\text{g}/\text{kg}$  and ribavirin. The issue of the appropriate non-inferiority margin became moot because the trial demonstrated superiority of peginterferon 1.5  $\mu\text{g}/\text{kg}$  and ribavirin over Rebetron.*

Treatment response was also evaluated at week 24 of the treatment period. This was defined as the time point for assessing the primary outcome for the registration dossier to be filed with the EU Health Authorities. The Health

Authorities evaluated the dossier and requested additional efficacy data at 3 months after the end of the treatment period. The analysis was modified to include this request. No adjustments to the  $\alpha$  were made for these additional analyses.

A step-down procedure was used to conserve the  $\alpha$  at 0.05. The primary comparison was PEG 1.5/R versus I/R using  $p=0.05$  (two-sided) as the level of significance. If this comparison was significant, then the comparison of PEG 0.5/R versus I/R would be made.

The primary analysis was to be performed using patients randomized and receiving at least one dose of study treatment. Confirmatory analyses would be performed using all randomized patients.

#### Secondary Efficacy Analyses

Pair-wise treatment differences were to be examined using logistic regression for the following endpoints listed in order of importance.

- Proportion of patients with normalization of ALT at 24 weeks of follow-up.
- Proportion of patients with undetectable HCV-RNA at the end of treatment.
- Proportion of patients with normalization of ALT at the end of treatment.

Pair-wise treatment differences were to be summarized for the following endpoints.

- Proportion of patients with improved biopsy scores (HAI I + II + III).
- Changes from baseline in biopsy scores (HAI I + II + III).
- Proportion of patients with improvement in biopsy score (HAI IV).
- Changes from baseline in biopsy scores (HAI IV).
- Proportion of patients with improved biopsy (METAVIR Activity Score).
- Changes from baseline in the biopsy scores (METAVIR Activity Score).
- Proportion of patients with improved biopsy (METAVIR Fibrosis Score).
- Changes from Baseline in the biopsy scores (METAVIR Fibrosis Score).

HQL was assessed using SF-36, generic scales (sleep, somnolence, general health distress [HDTS], and mental health inventory) and hepatitis C specific scales (hepatitis C health distress [HDTS] and hepatitis C limitations). The vitality component of the SF-36 and the generic and hepatitis C specific scales, particularly GHDTS and HHDTS, would be the focus of the full quality life evaluation. The study had a power of 90% ( $\alpha = 0.05$ , two-sided) to detect a difference of 5 points in the scores.

The primary analysis was a comparison of the two treatment groups, 1.5  $\mu\text{g}/\text{kg}$  PEG-IFN QW + 800 mg ribavirin versus interferon alfa-2b + ribavirin, using repeated measurement models, supplemented by analysis of variance model for each visit during the follow-up period. Baseline was included in the model as a covariate. Other baseline characteristics could be included in the model if imbalances were present at baseline.

## STUDY CENTERS

Clinical Investigators from 62 clinical centers participated in the study. The US contributed approximately half of the total study centers and approximately 2/3 of total study patients. The non-US centers were located in the following regions. Participating centers from the Americas were located in Canada (6 centers), and Argentina (2 centers). Participating centers from Europe were located in: France (8 centers), Germany (5 centers), Spain (4 centers), Sweden (2 centers), Austria (2 centers), and Greece (1 center).

## PATIENT DISPOSITION

Approximately 500 patients per treatment group were randomized and received at least one dose of study treatment (see **Table 6**). The protocol specified that these patients would be defined as the intent-to-treat population for the purpose of the primary efficacy analysis. Fifty patients were randomized but received no treatment; the highest number of these patients was in the interferon/ribavirin treatment arm. Approximately 20% of patients across all treatment groups did not complete the study.

**Table 6. Disposition of All Randomized Subjects**

Disposition	Treatment Groups			Totals
	Peg-IFN 1.5µg/kg Riba 800 mg	Peg-IFN 0.5µg/kg Riba1000/1200 mg	IFN 3x10 <sup>6</sup> U Riba1000/1200 mg	
Randomized	524	530	526	1580
Randomized and treated	511 (98)	514 (97)	505 (96)	1530
Randomized but not treated	13	16	21	50
Completed treatment	411 (80)	422 (82)	397 (79)	1230
Completed treatment and follow-up	399 (78)	412 (80)	387 (77)	1198

Numbers in parentheses are percentages

The main reason for the non-treatment of randomized subjects was a decision of the subject not to participate in the study after the treatment allocation for this open-label study became known (see **Table 7**).

**Table 7. Accounting for Randomized Untreated Subjects**

Subject's choice	Loss to follow up	Non-compliance	Non-eligibility	Administrative problem
36	1	5	5	3

*Reviewer's comments*

*The number and the main reason for non-treatment of randomized subjects by treatment group shows some bias in favor of the experimental treatment probably due to the un-blinded design of the study. As a result, the protocol definition of the ITT population (participant randomized and received  $\geq 1$  treatment) is reasonable. The overall numbers of non-treated subjects and the differences in the distribution of non-treated subjects across treatment groups are small. Analysis of the data using all randomized subjects does not affect the primary efficacy outcome (see efficacy analyses).*

*A few of the non-treated patients were misclassified as to the reason for being untreated. For example six patients who withdrew their consent to participate in the study because of treatment assignment were classified by the sponsor as lost to follow up or non-eligible. The proportion of patients (20%) who did not complete the study is high and is in line with other studies of interferon alpha. Most of these patients were discontinued from treatment due to adverse events (see safety data).*

**PATIENT DEMOGRAPHICS**

Age, gender, ethnic origin, and body weight were evenly distributed across treatment groups (see **Table 8**).

**Table 8. Demographics**

	PEG 1.5/R	PEG 0.5/R	I/R
<b>Age (years)</b>			
Mean	44	44	43
Range	21-68	22-67	22-68
<b>Gender</b>			
Women	190 (37)	168 (33)	169 (34)
Men	321 (63)	346 (67)	336 (66)
<b>Ethnic origin</b>			
Caucasian	465 (91)	453 (88)	448 (89)
Black	22 (4)	28 (5)	25 (5)
Asian	5 (1)	5 (1)	8 (2)
Hispanic	12 (2)	23 (4)	13 (3)
Other	7 (1)	5 (1)	11 (2)
<b>Body Weight (kg)</b>			
Mean	82	83	82
Range	43-159	38-181	43-163

Numbers in parentheses are percentages

The mean age of study participants was approximately 44 years and this mean is within the age group (30-49 years of age) with the highest HCV prevalence in the US. The study protocol excluded pediatric patients. The upper age limit for the study was 70 years due to generally less favorable risk/benefit of interferon alphas in patients with advanced age. Very few elderly subjects were studied.

The mean body weight of participants was approximately 82 kg and ranged from 38 to 181 kg. The distribution towards larger body weights and the wide range in weights resulted in a wide range of exposures to ribavirin. In contrast to the weight-adjusted administration of interferon and peginterferon, ribavirin as per protocol was weight-adjusted either crudely (based on body weight above or below 75 kg) or not at all (the latter in the PEG 1.5/R group).

Approximately 2/3 of the participants were men. This gender distribution is consistent with the higher prevalence of HCV in men. Approximately 90% of participants were of Caucasian origin. Since the prevalence of HCV in the US is higher in African Americans and in Hispanics compared to Caucasians, these two ethnic minorities were under-represented in the study.

*Reviewer's comments*

*A study of peginterferon monotherapy showed that response to interferon treatment of HCV was numerically lower in African Americans and Hispanics compared to Caucasians. The reasons are not well understood and may be at least in part related to differences in prognostic factors in the minority patients entered into the study. Given the higher prevalence of HCV in minority groups and apparently poorer treatment responses additional studies of peginterferon/ribavirin in these minorities are needed.*

**DISEASE CHARACTERISTICS AT BASELINE**

Source of HCV infection

The source of HCV infection and the duration of infection were similar across treatment groups (see **Table 9**). The main source of HCV in the participants of the study was parental exposure. This is consistent with what is still the main mode of transmission of HCV, namely injection of illicit drugs. The second highest source of HCV in the participants was transfused blood products reflecting the relatively high incidence of infection before HCV screening of blood products became available. Approximately 15% of participants had other causes or non-recognized sources of infection.

**Table 9. Source of HCV Infection**

	PEG1.5/R	PEG 0.5/R	I/R
Transfusion products	114 (22)	105 (20)	101 (20)
Parenteral	315 (62)	337 (66)	326 (65)
Sporadic/other	82 (16)	72 (14)	78 (15)

Numbers in parentheses are percentages

### Duration of HCV infection

In the participants for whom information on exposure was available, the duration of infection was estimated from the time of exposure to a source of HCV. The mean duration of infection was approximately 19 years in the three treatment groups. The duration ranged from less than 1 year to 51 years (see Table 10).

**Table 10. Duration of Infection**

	PEG1.5/R N=439	PEG 0.5/R N=449	I/R N=432
<b>Years from exposure</b>	20 (<1 – 51) <sup>1</sup>	19 (<1 - 48)	19 (<1 - 47)

<sup>1</sup>Means (range)

### Viral genotype and viral load

Approximately two thirds of participants in the study were infected with genotype 1 and this is consistent with the incidence of this genotype in infected patients in the US. Infection with genotypes 4-6 was rare.

No relationship has been shown between rate of progression or severity of liver disease and the HCV genotype or the number of circulating HCV-RNA copies. Both viral genotype and load are known predictors of response to interferon treatment. Patients infected with viral genotype 1 and high viral load (defined as > 2X10<sup>6</sup> RNA copies/ml serum) are least likely to respond to interferon treatment. The proportion of patients with these two specific prognostic viral characteristics was similar in the three treatment groups (see Table 11).

**Table 11. Viral Genotype and Viral Load at Baseline**

	PEG 1.5/R N=511	PEG 0.5/R N=514	I/R N=505
<b>HCV genotype</b>			
1	348 (68)	349 (68)	343 (68)
2	83 (16)	71 (14)	65 (13)
3	64 (12)	82 (16)	81 (16)
4	15 (3)	9 (2)	15 (3)
5	1 (<1)	1 (<1)	0
6	0	2 (<1)	1 (<1)
<b>HCV RNA copies/ml</b>			
≤ 2 x10 <sup>6</sup>	160 (31)	169 (33)	161 (32)
>2 x10 <sup>6</sup>	351 (69)	345 (67)	344 (68)

Numbers in parentheses are percentages

### Severity of liver disease at baseline

Evidence of active liver disease that is progressing towards cirrhosis is generally required for interferon treatment. With rare exceptions participants at baseline had

elevated levels of transaminases and evidence of liver fibrosis on liver biopsy. A baseline liver biopsy was missing in 5-8 percent of patients.

Five to seven percent of patients had compensated cirrhosis. Patients with cirrhosis are less likely to respond to interferon treatment. The presence of decompensated cirrhosis is a contraindication to interferon treatment. Around 20% of patients had evidence of bridging of portal and central veins by fibrous tracts. Thus around 25% of the participants had evidence of advanced liver disease (bridging fibrosis or cirrhosis) by liver biopsy. The biopsy also showed evidence of active inflammation and necrosis. The two histologic scoring systems used (Knodell and Metavir) yielded similar results.

As with other disease characteristics there was no imbalance between groups in the severity of liver disease (see **Table 12**).

**Table 12. Severity of Liver Disease at Baseline**

	PEG(1.5)/R N=511	PEG 0.5/R N=514	I/R N=505
<b>ALT/ALT-ULN</b>			
Mean	3	3	3
Range	<1-13	1- 20	1-22
<b>Hepatic fibrosis</b>			
None	8 (2)	0	7 (1)
Portal	325 (64)	345 (67)	329 (65)
Bridging	102 (20)	114 (22)	109 (22)
Cirrhosis	34 (7)	32 (6)	23 (5)
Missing	42 (8)	23 (5)	37 (7)

Numbers in parentheses are percentages. ULN: Upper Limit of Normal.

The sponsor determined that after taking into account protocol-required dose-modifications the compliance to study treatments was very high.

### **PRIMARY EFFICACY ANALYSES**

The primary efficacy analysis was a logistic regression analysis with main effects due to treatment, genotype (dichotomized as genotype 1 vs. non-1), and presence of cirrhosis at baseline. The primary comparison was between the PEG 1.5/R and the I/R groups. The intent-to-treat population for the efficacy analyses was defined as randomized patients who received at least one dose of study treatment.

ITT analyses using all randomized patients gave results similar to those using the protocol-defined ITT population. The absolute difference in the proportion of responders between PEG 1.5/R and I/R was 6%. Treatment responses using both efficacy populations are shown in **Table 13**.

**Table 13. Treatment Response at Week 24 Post-treatment**

HCV RNA	Treatment Groups		
	Peg-IFN 1.5 Riba 800	Peg-IFN 0.5 Riba 1000/1200	IFN 3x10 <sup>6</sup> U Riba1000/1200
	<b>Randomized Patients</b>		
Negative	264 (50)	239 (45)	231 (44)
Positive	185 (35)	214 (40)	203 (39)
Missing	75 (14)	77 (15)	92 (17)
TOTAL	524	530	526
	<b>Randomized Treated Patients</b>		
Negative	264 (52)	239 (46)	231 (46)
Positive	185 (36)	214 (42)	203 (49)
Missing	62 (12)	61 (12)	71 (14)
TOTAL	511	514	505

*Response is defined as loss of HCV RNA detection. The numbers in parentheses are percentages.*

A test of non-inferiority, using confidence intervals around treatment differences adjusted for the stratification factors was performed in the pre-specified statistical analysis plan. The non-inferiority margin was pre-specified to be 10% of the response rate in the standard treatment arm (I/R). Treatment response was 45.7% in the I/R group with a 10% non-inferiority margin of -4.57%. The primary comparison, namely PEG 1.5/R vs. I/R, showed a treatment difference of 6% (C.I. 0.18%, 11.6%), thus demonstrating superiority of the experimental treatment. For the comparison of PEG 0.5/R vs. I/R, the treatment difference was 1% (C.I. - 4.7%, 6.5%).

An unadjusted analysis using an overall comparison of treatment responses in the three groups showed no significance ( $P = 0.1$ ), while a comparison of the PEG 1.5/R vs. the I/R group showed marginal significance ( $P = 0.06$ ). Controlling for viral genotype at baseline resulted in a  $P$  value of 0.03 for the comparison between the PEG1.5/R and the I/R groups.

Controlling for baseline cirrhosis did not affect the level of significance. Five pre-treatment biopsies were read by the central pathologist but were erroneously not included in the database before lock. The local pathologist's assessment of cirrhosis at baseline was used. Upon review it was determined that the local and central assessors agreed on the diagnosis for all five cases. According to the sponsor there was 90% concordance between the local (roughly 60) pathologists and the single central pathologist in the diagnosis of cirrhosis at baseline. Using the diagnosis of either the local or central assessor did not affect the  $P$  value.

*Reviewer's comments*

*In the proposed package insert the sponsor cites the following treatment responses (See table below).*

The package insert will list estimates of treatment effect derived from the protocol-specified primary efficacy analysis.

## SECONDARY EFFICACY ANALYSES

### ALT Normalization; HCV RNA at end of treatment

The normalization of serum ALT (biochemical response) at the end of the follow up period was the principal secondary endpoint. The estimates of treatment response using ALT measurements are consistent with the results obtained using HCV RNA detection (see **Table 15**).

**Table 15. Normalization of Serum ALT**

	<b>PEG (1.5)/R</b>	<b>PEG 0.5/R</b>	<b>I/R</b>
End of Follow Up	54% <sup>1</sup> (274)	48% (247)	47% (236)
End of Treatment	65% (332)	63% (326)	69% (350)

<sup>1</sup>Proportion of patients with normalization of ALT

Virologic responses and biochemical responses at the end of treatment period were the two other pre-specified secondary outcomes. The proportion of patients with normalization of ALT at the end of the treatment period was not higher in the peginterferon-treated groups (see **Table 15**). On the other hand, the proportion of patients with undetectable HCV RNA at the end of the treatment period was higher in the PEG1.5/R arm compared to the I/R arm (see **Table 16**). As shown in

previous studies, after discontinuation of treatment a number of patients experience a relapse of the infection and HCV RNA becomes again detectable.

**Table 16. Loss of Detection of HCV RNA at the End of the Treatment Period**

HCV RNA Wk 48 End of treatment	PEG (1.5)/R N	PEG 0.5/R N	I/R N
Negative	333	289	271
Positive	158	202	202
Missing	33	39	53
Total	524	530	526
<b>RESPONDERS</b>	64%	55%	52%

The cross correlation between virologic response (loss of detection of HCV-RNA) and biochemical response (normalization of ALT levels) at the end of the follow up period was very high (see Table 17).

**Table 17. Cross Correlation between Virologic and Biochemical Response at End of Follow up Period**

HCV RNA	Alanine aminotransferase							
	PEG (1.5)/R				I/R			
	WNL	≤2X ULN	>2X ULN	Missing	WNL	≤2X ULN	>2X ULN	Missing
Negative	256(97)	5 (2)	0	3(1)	223(97)	6(2)	2(1)	0
Positive	18 (10)	91(49)	75 (41)	1(1)	13(6)	106(53)	94(41)	0

WNL: Within Normal Limits. ULN: Upper Limit of Normal.  
Numbers in parentheses are percentages.

#### Liver histopathology

Another secondary outcome of interest was improvement in liver histopathology at 24-week post-treatment. Paired liver biopsies were obtained before and after treatment in 68% of patients. Response to treatment based on Histologic Activity Score (a measure of inflammatory changes in the liver) was defined as ≥2 point decrease in score from baseline. Approximately two thirds of patients in all treatment groups were observed to have a modest reduction in inflammation compared to baseline (see Table 18). Approximately 20% of patients had no change in inflammation score, and 10% had an increase ≥2 points in inflammation score. There were no differences between treatment groups.

Response to treatment based on Knodell IV score (a measure of liver fibrosis) was observed in about 20% of patients in all treatment groups. Approximately 70% of patients had no change in fibrosis score and 10% of patients had an increase in fibrosis score. There were no differences between treatment groups.

**Table 18. Liver Inflammation and Fibrosis at 24 Weeks Post-Treatment**

	PROPORTION OF PATIENTS WITH LOWER SCORES COMPARED TO BASELINE		
	PEG 1.5/R N= 339	PEG 0.5/R N=361	I/R N=334
Inflammation (HAI I-III score)	68%	70%	69%
Fibrosis (HAI IV)	21%	19%	20%

Health-related quality of life was assessed by a self-administered questionnaire. Scores for all groups decreased numerically during treatment and returned to baseline at the end of the post-treatment observation period. No significant differences were observed.

### SUBGROUP ANALYSES

Subgroup analysis: patients who relapse in the post-treatment period

Patients with HCV-RNA undetectable at the end of treatment but detectable at 24 weeks post-treatment were considered to have relapsed. The proportion of patients who relapsed (had positive or missing HCV RNA) appeared to be numerically highest (21%) in the Peg 1.5/R group (see Table 19).

**Table 19. Relapse in Patients with Undetectable HCV RNA at End of Treatment**

HCV RNA at week 24 post-treatment	PEG 1.5/R N= 333	PEG 0.5/R N=289	I/R N=271
Positive	48	37	33
Missing	23	13	8
Negative	262	239	230
Relapsed <sup>1</sup>	21%	17%	15%

<sup>1</sup>Relapsed = Positive+ Missing/Total

Across all treatment groups, the incidence of relapse (at the end of the 24-week post-treatment period) was numerically higher (2 to 3-fold) in patients with HCV genotype 1 compared to patients with other HCV genotypes.

*Reviewer's comments*

The proportion of treatment-naïve patients who relapse after interferon monotherapy is high (around 50%). The proportion of naïve patients who relapse after interferon/ribavirin therapy is much lower and this study confirmed that observation.

Subgroup analysis: time to first loss of HCV RNA in treatment responders

The proportion of treatment responders who achieve loss of HCV RNA by week 12 of treatment is approximately 90% in the I/R group and 95% in the Peg/R groups. By week 24 nearly all treatment responders were HCV- RNA negative. **Table 20** shows that the rare treatment responder who was still HCV positive by week 24 had low circulating levels of virus.

**Table 20. Treatment Responders with First Response After Week 24**

	Peg 1.5/R	Peg 0.5/R	I/R
Number of responders with first response after week 24	1	0	3
Highest HCV RNA level (copies/ml serum)	1,400,000	0	4,500

*Reviewer's comment*

The time to response data in this study are consistent with the data from the peginterferon monotherapy study.

Subgroup analysis: treatment response by viral genotype and load at baseline.

Patients with viral genotype 1, regardless of viral load, had a lower response rate compared to patients with other viral genotypes. Patients with high viral load ( $>2 \times 10^6$  copies of HCV RNA/ml serum) also had lower response rates compared to patients with low viral load (see **Table 21**).

**Table 21. Response to Treatment by Viral Genotype and Viral Load**

	PEG 1.5/R	I/R
<b>Genotype 1</b>	141/348 (41%) <sup>1</sup>	112/343 (33%)
<b>Genotype 2-6</b>	123/163 (75%)	119/162 (73%)
<b>Viral load <math>\leq 2 \times 10^6</math>/ml</b>	121/160 (75%)	89/161 (55%)
<b>Viral load <math>&gt;2 \times 10^6</math>/ml</b>	143/351 (41%)	142/344 (41%)

<sup>1</sup>Proportion of responders

Patients with both genotype 1 and high viral load were least likely to respond both in the PEG 1.5/R group (30%, 78/256) and in the I/R group (29%, 71/247).

*Reviewer's comments*

Data from this study and previous studies show that patients in certain subgroups (e.g. non-genotype 1 with or without low viral titers; genotype 1 and low viral titers) have: 1) higher proportion of responders, and 2) early ( $\leq 3$  months) and stable loss

of HCV RNA in a very high proportion of treatment responders. These observations suggest that treatment duration < 12 months is likely to be efficacious and safer in these patient subgroups. Studies should be conducted to evaluate the efficacy of a shorter duration of peginterferon/ribavirin treatment in treatment-naive patients with chronic HCV hepatitis, low viral titers at baseline, and/or HCV genotypes 2 and 3.

Subgroup analysis: response to treatment by presence of hepatic fibrosis

Patients with advanced hepatic fibrosis (bridging fibrosis or cirrhosis and scores of 3 or 4 respectively in Knodell's HAI IV) had numerically lower response rates compared to patients with mild or no fibrosis (scores of 0-1). The number of patients with cirrhosis (score of 4) was too low to draw conclusions on treatment responses in this subgroup; 5-8% of patients had missing biopsies at baseline. In two of the larger subgroups, the responses to treatment across the three study arms tended to favor PEG 1.5/R (see Table 22).

**Table 22. Response to Treatment by Presence of Advanced Hepatic Fibrosis**

	Histologic Activity Index IV		
	0-1	3-4	4
<b>PEG 1.5/R</b>	180/333 (54) <sup>1</sup>	60/136 (44)	11/34 (32)
<b>PEG 0.5/R</b>	170/345 (49)	63/146 (43)	14/32 (44)
<b>I/R</b>	161/336 (48)	53/132 (40)	11/23 (46)

<sup>1</sup>Proportion of responders

Subgroup analysis: response to treatment by age, gender, and ethnic group

Age of Study Subjects.

In general, younger patients appeared to respond better than older patients (see Table 23). The study did not include sufficient numbers of subjects aged 65 and over, however, to determine whether geriatric patients respond differently than younger subjects. No pediatric subjects were studied.

**Table 23. Response to Treatment by Age**

	≤35 <sup>1</sup>	35-44	45-54	55-64	≥65
<b>PEG1.5/R</b>	39/62 (63)	115/216 (53)	90/187 (48)	19/42 (45)	1/4 (25)
<b>I/R</b>	48/72 (67)	82/200 (41)	79/191 (41)	21/39 (54)	1/3 (33)

<sup>1</sup>Years of age

The numbers in parentheses are percentage of responders

Gender and Ethnic Origin.

Treatment response rates with PEG-Intron/REBETOL were 49% in men and 56%

in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Subgroup Analysis: response to treatment by geographic region

Approximately two third of study patients were enrolled in the US. The other patients were enrolled in Europe, Canada and Argentina. **Table 24** shows that overall the proportion of responders was numerically higher in patients enrolled at non-US centers compared to patients at US centers. In the I/R arm the difference in treatment response between US and non-US centers was significant. The difference was significant even after adjusting for HCV genotype and titer, liver fibrosis, and body weight.

For patients enrolled in the US the proportion of responders was highest in the Peg 1.5/R arm. The odds ratio for the difference in treatment response between the I/R and Peg 1.5/R arms in the US was 0.66 (C.I. 0.49 – 0.9) reflecting the lower likelihood of patients in the Peg 1.5 arm to remain HCV-RNA positive.

In patients enrolled in non-US centers the treatment responses between study arms were not different.

**Table 24. Proportion of Responders by Geographic Region**

	Peg 1.5	IPEG 0.5	I/R
US	169/346 (49%)	154 /343 (45%)	131/337 (39%)
Non-US	95/165 (57%)	85/171 (50%)	100/168 (59%)

**Table 25** shows that In the US the lower response rates were associated with higher proportion of patients with less favorable prognostic factors at baseline. These factors are HCV genotype 1, high viral load, and presence of liver fibrosis. Advanced liver fibrosis was defined as presence of cirrhosis or bridging fibrosis corresponding to Knodell fibrosis scores of 3 or 4. Baseline biopsies were missing in as many as 10% of patients in both geographic regions.

In the present study an inverse correlation existed between body weight and treatment response. **Table 25** shows that body weight was also higher in the US patients.

**Table 25. Prognostic Factors in Geographic Subgroups at Baseline**

	Fibrosis Score <sup>1</sup>		HCV-1 <sup>1</sup>	HCV-RNA <sup>2</sup> copy/ml serum	Body weight <sup>2</sup> kg
	Grade 3	Grade 4			
US	245 (23%)	74 (7%)	769 (72%)	4.2X10 <sup>6</sup> (600- 51X10 <sup>6</sup> )	85 (43-181)
Non-US	79 (15%)	15 (3%)	305 (60%)	1.7X10 <sup>6</sup> (7,400- 50x10 <sup>6</sup> )	74 (38 -131)

<sup>1</sup>Number of study subjects (percentages)<sup>2</sup>Medians (min-max)**Subgroup analysis: treatment response by body weight**

The distribution of body weights in patients in the US was different than that of patients in other regions. The body weights in the two regions were grouped by quartiles for the analysis of response to treatment shown in the **Tables 26-27** below.

Differences in response rates between treatment arms varied somewhat with body weight. Patients with lower body weight tended to have higher response rates than patients with higher body weights.

**Table 26. Treatment Response by Baseline Weight in Patients in US Centers**

Body weight quartiles (kg)	PEG 1.5/R	PEG 0.5/R	I/R	Total <sup>1</sup>
≤ 74	51/93 (55)	41/89 (46)	28/75 (37)	257
>74 ≤85	45/86 (52)	34/79 (43)	40/92 (43)	260
>85 ≤98	37/86 (43)	38/78 (49)	46/97 (47)	261
> 98	36/81 (44)	42/94 (45)	17/74 (23)	249

<sup>1</sup>Number of patients in each weight group

Numbers in parentheses are percentage of responders

**Table 27. Treatment Response by Baseline Weight in Patients in non-US Centers**

Body weight quartiles (kg)	PEG 1.5/R	PEG 0.5/R	I/R	Total <sup>1</sup>
≤ 64	25/36 (69)	23/45 (51)	32/61 (52)	132
>64 ≤74	23/42 (55)	25/43 (58)	29/40 (72)	125
>74 ≤84	21/40 (52)	18/38 (47)	22/44 (50)	122
> 84	26/47 (55)	19/45 (42)	17/33 (52)	125

<sup>1</sup>Number of patients in each weight group

Numbers in parentheses are percentage of responders

A number of factors could account for this apparent interaction between body weight and treatment response. The different response rates may, for example, be due to differences in exposure to study drugs due to insufficient or no adjustment of dose for body weight. In the PEG1.5 group patients received a fixed dose (800 mg) of ribavirin, in the IFN/R group patients received a fixed dose of interferon.

To explore this issue further the sponsor analyzed treatment response by daily dose of ribavirin normalized by body weight (mg/kg). Logistic regression analyses showed that the probability of response was a function of ribavirin daily dose per body weight. From these analyses the sponsor concluded that  $13 \pm 2$  mg/kg is the optimal dose of ribavirin to administer with peginterferon 1.5  $\mu$ g/kg.

The sponsor analyzed the response rate in the PEG1.5/R group using as a cutoff a daily dose of ribavirin of 10.6 mg/kg. The selection was arbitrarily based on the dose a patient with "average" body weight (75 kg) would receive. These analyses showed that treatment responses were numerically higher in patients who received more than 10.6 mg/kg/day of ribavirin.

In the C96-114 study, interferon-naïve subjects were treated for 6 months with either 800 or 1000/1200 mg/day of ribavirin in combination with INTRON A. The sustained response rate was numerically higher in the INTRON A + ribavirin 1000/1200 mg/day group compared to the INTRON A + ribavirin 800 mg/day group (27% vs. 23%). An analysis was done with subjects categorized as being on 'high' or 'low' ribavirin regimens depending on whether they received more or less than 11 mg/kg/day of ribavirin. The 11mg/kg break point was selected as it represents a dose of approximately 800 mg for an "average weight" (75 kg) subject. Using this categorization, the sustained response rates were 31% and 22% for 'high' and 'low' ribavirin regimens.

Based on these exploratory analyses of the present efficacy trial and other trials, the sponsor proposed that ribavirin be administered on a weight-adjusted basis to patients with chronic hepatitis C (see **Table 28**).

**Table 28. Sponsor's Proposal for REBETOL Dosing**

Body weight kg (lbs)	REBETOL mg/day	REBETOL Number of Capsules
—	[	]
40-64 —	800	2 x 200 mg capsules AM, 2 x 200 mg capsules PM
65-85 —	1,000	2 x 200 mg capsules AM, 3 x 200 mg capsules PM
86-105 —	1,200	3 x 200 mg capsules AM, 3 x 200 mg capsules PM
>105 —	1,400	3 x 200 mg capsules AM, 4 x 200 mg capsules PM

The sponsor analyzed safety data based on a dichotomized ribavirin dose ( $\leq 10.6$  or  $> 10.6$  mg/kg). These analyses showed that the incidence of adverse events known to be induced by ribavirin (e.g. anemia) was numerically higher in the  $> 10.6$  mg/kg group. The incidence of adverse events not attributable to ribavirin (e.g. neutropenia) was also numerically higher in the  $>10.6$  mg/kg subgroup group. Moreover, the incidence of dose modifications for adverse events was also higher in this subgroup.

The sponsor hypothesizes that weight-based dosing of ribavirin would not increase the risk of serious adverse events. Ribavirin toxicities detected promptly by clinical observations and laboratory testing might be reversible and might be managed by reducing ribavirin dosage

*Reviewer's comments*

*The sponsor concludes that ribavirin should be administered on a weight-adjusted basis to achieve optimal treatment response. The sponsor provided a rationale for this proposal based on post-hoc analyses of the clinical efficacy data. It could not be determined from a review of the sponsor's analyses why a  $13\pm 2$  mg/kg ribavirin dosage was judged to be optimal. It was also unclear why the sponsor had proposed doses  $\geq 16$  mg/kg in patients weighing  $\leq 50$  kg.*

*The agency determined that the sponsor did not provide an adequate pharmacokinetic and risk/benefit justification for the doses of ribavirin he proposed. The agency requested that the sponsor provide additional analyses of PK data and of clinical safety and efficacy data to better judge the risk benefit of weight-adjusted ribavirin doses. The agency requested prospectively designed trial to address this issue and such trials are now ongoing.*

Exploratory analysis: treatment response by ribavirin dosage (mg/kg)

For these exploratory analyses the patients in the study were categorized arbitrarily by dividing the distribution of ribavirin dosages into quartiles. Caution is needed in interpreting the results of these analyses because of small patient numbers and imbalance in the patient numbers between quartiles and across study arms within the same quartile. More importantly, the comparison of the outcome data by ribavirin dosage may be confounded by differences known (e.g. body weight) or unknown between these non-randomized groups.

Treatment responses by ribavirin dose administered/ body weight /day were examined in the patient subgroups shown in **Table 29**. All treated patients were included in the analyses. The proportion of responders was higher in subgroups with higher ribavirin dose/weight ratios.

**Table 29. Treatment Response by Ribavirin Dosage**

Ribavirin dosage quartiles	PEG 1.5/R	PEG 0.5/R	I/R
> 14.7 <sup>1</sup>	13/21 (62) <sup>2</sup>	76/171 (44)	99/184 (54)
>13.3 - ≤ 14.7	25/38 (67)	91/174 (52)	75/170 (44)
≥10.7 - ≤ 13.3	70/126 (56)	58/134 (43)	50/126 (40)
<10.7	156/326 (48)	14/35 (40)	7/25 (28)
<b>Ribavirin dosage median (range)</b>	9.8 (5-19) <sup>3</sup>	13.9 (7-26)	14.2 (7-23)

<sup>1</sup> mg/kg (daily ribavirin dose/body weight at baseline); <sup>2</sup> percentage of responders; <sup>3</sup> numbers are medians, minimum and maximum values in mg/kg.

The proportion of responders was higher in the higher ribavirin dose groups even after controlling for HCV genotype, high ( $\geq 2 \times 10^6$  copies/ml serum) or low HCV RNA, and gender in the analyses (not shown).

Exploratory analysis: safety outcomes by ribavirin dosage (mg/kg)

The potential for higher numbers of treatment responders with higher ribavirin doses must be considered together with the potential for higher ribavirin toxicity. For this reason exploratory analyses of selected safety outcomes by ribavirin dosage are presented in this section.

**Dose Modification or Discontinuation of Study Treatment**

The incidence of dose modification due to adverse events was numerically higher in patients in the PEG1.5/R and the I/R arms who had higher daily ribavirin dose/body weight ratios (see **Table 30**). Patients who discontinued treatment due to adverse events were not included in this analysis.

**Table 30. Modification of Dose of Study Treatment by Ribavirin Dosage and Treatment Group**

Ribavirin dosage mg/kg/day	PEG 1.5/R	PEG 0.5/R	I/R
> 14.7	8 (47) <sup>1</sup>	57 (40)	65 (41)
>13.3 - ≤ 14.7	31 (61)	70 (32)	68 (31)
≥10.7 - ≤ 13.3	54 (45)	44 (36)	33 (31)
<10.7	124 (38)	14 (44)	4 (18)

<sup>1</sup> number (percentage) of patients with reduction of interferon or ribavirin dose

Table 31 shows that the in the PEG 1.5/R arm, the incidence of dose modification appeared to be numerically higher in the higher ribavirin dosage subgroups in the following body systems: Central and peripheral Nervous System (CNS/PNS), Endocrine, Blood Clotting, Red Blood Cell, White Cell and Skin. The number of events is small and interpretation must be cautious.

**Table 31. Modification of Dose of Study Treatment by Ribavirin Dosage and Body System in the PEG 1.5/R Arm.**

Body system	Ribavirin Dosage mg/kg/day			
	<10.7	≥10.7 ≤ 13.3	>13.3 ≤ 14.7	> 14.7
Application Site	0	0	1(2)	0
Body as a Whole	29 (9) <sup>1</sup>	15 (13)	3 (6)	1 (6)
CNS/PNS	8 (2)	4(1)	1(1)	3 (6)
Endocrine	1 (0.3)	1(1)	1(2)	0
Heart Rate/ Rhythm	1 (0.3)	0	1(2)	0
Musculoskeletal	7(2)	3(3)	0	0
Platelet Bleeding/Clotting	12 (4)	7 (6)	4 (8)	1 (6)
Psychiatric	12 (4)	7 (6)	4 (8)	1(6)
Red Blood Cell	22 (7)	12 (10)	8 (16)	2 (12)
Resistance Mechanism	2 (0.6)	4 (3)	0	0
Respiratory	5 (2)	1 (1)	1 (2)	0
Skin/Appendage	7 (2)	2 (2)	2 (4)	1 (6)
Vision	2 (0.6)	1 (1)	0	0
White Cell/RES	51 (16)	26 (22)	11 (22)	4 (24)

<sup>1</sup> number (percentage) of patients

Table 32 shows numerically higher incidence of dose modifications across all three study arms in the higher ribavirin dosage groups (mg/kg/day) for anemia and neutropenia.

**Table 32. Modification of Dose of Study Treatment for Hematologic Toxicity by Ribavirin Dosage and Study Arm**

Ribavirin dosage mg/kg/day	PEG 1.5/R	PEG 0.5/R	I/R
	Anemia		
> 14.7	2 (12) <sup>1</sup>	29 (40)	31(20)
>13.3 - ≤ 14.7	8 (16)	24(11)	28(13)
≥10.7 - ≤ 13.3	12 (10)	9 (7)	7 (7)

<10.7	22 (7)	2 (6)	1 (5)
	Neutropenia		
> 14.7	4 (24)	14 (10)	17 (11)
>13.3 - ≤ 14.7	10 (20)	21 (10)	15 (7)
≥10.7 - ≤ 13.3	26 (22)	12 (10)	6 (6)
<10.7	51 (16)	2 (6)	0

Numbers in parentheses are percentages

The overall incidence of dose discontinuation was numerically similar across ribavirin dose groups and study arms. Discontinuations for anemia and neutropenia were numerically higher in the higher ribavirin doses in the three study arms (not shown).

#### Adverse Events by Ribavirin Dosage

The incidence of anemia and neutropenia was numerically higher in the higher ribavirin dose subgroups (mg/kg/day) across the three study arms. The incidence of thrombocytopenia appeared to also follow the same upward trend with higher ribavirin dose in the PEG1.5/R and the I/R arms of the study (see **Table 33**).

**Table 33. Incidence of Hematologic Adverse Events by Ribavirin Dosage and Study Arms**

Ribavirin dosage mg/kg/day	PEG 1.5/R		PEG 0.5/R		I/R	
	All Grades	Severe/LT <sup>1</sup>	All grades	Severe/LT	All grades	Severe/LT
	anemia					
> 14.7	3 (18)	0	40 (28)	2 (1)	41 (26)	3 (2)
>13.3 - ≤ 14.7	16 (31)	1 (2)	32 (15)	1 (0.5)	35 (16)	0
≥10.7 - ≤ 13.3	15 (13)	0	14 (12)	0	8 (8)	0
<10.7	27 (8)	0	3 (9)	1 (3)	2 (9)	0
	neutropenia					
> 14.7	8 (47)	4 (24)	29 (20)	9 (6)	30 (19)	9 (6)
>13.3 - ≤ 14.7	15 (29)	6 (12)	27 (12)	12 (5)	28 (13)	10 (5)
≥10.7 - ≤ 13.3	37 (31)	14 (12)	20 (17)	9 (7)	10 (9)	4 (4)

<10.7	74 (23)	28 (9)	2 (6)	2 (6)	1 (5)	0
	thrombocytopenia					
> 14.7	1 (6)	0	2 (1)	0	6 (4)	0
>13.3 - ≤ 14.7	4 (8)	0	2 (1)	0	3 (1)	0
≥10.7 - ≤ 13.3	3 (3)	0	4 (3)	1 (1)	1 (1)	0
<10.7	20 (6)	0	3 (9)	0	0	0

<sup>†</sup> Life-threatening

Numbers in parentheses are percentages

### Reviewer's comments

The safety data suggest that with increasing ribavirin dosage higher proportions of patients experience adverse events. There may be a breakpoint in the increase in toxicity at ribavirin dosages >13 mg/kg/day. At these dose levels the majority of patients (around 60%) required dose modification for adverse events. The rise in incidence of hematologic toxicities (anemia, neutropenia, and thrombocytopenia) seems also steeper at >13 mg/kg/day of ribavirin dosage (see **Tables 30, 32, and 33**).

The schedule of clinical and laboratory assessment of patients during the trial was optimal and the protocol contained conservative rules for dose modification for a number of well known potentially serious and life-threatening adverse events induced by interferon and ribavirin (e.g. neutropenia and anemia). As is true for other clinical conditions, therapy of patients with chronic hepatitis C is likely to be less rigidly controlled and more uneven outside of clinical trials.

Less timely dose-modifications for adverse events may result in more toxicities observed post-marketing (more severe, more frequent) than that observed premarketing. The weight-based ribavirin dosing proposed by the sponsor may reasonably be expected to further increase the incidence of adverse events.

In view of the dose-dependent toxicities of ribavirin more studies are needed to optimize the ribavirin dose. Patients with lower than average body weight should be followed carefully for interferon and ribavirin-induced toxicities.

## SAFETY ANALYSES

### Discontinuation of study treatment

Adverse events were the main reason for discontinuation of study treatment. The incidence of all-cause discontinuation was numerically lower in the second half of the treatment period (see **Table 34**).

**Table 34. Reasons for Treatment Discontinuation Before and After Six Months of Treatment**

<u>Disposition</u>	<u>Treatment Groups</u>		
	PEG 1.5/R N=511	PEG 0.5/R N=514	I/R N=505
<b>Discontinued by six months</b>	<b>69 (14)</b>	<b>56 (11)</b>	<b>66 (13)</b>
Death	0	1 (<1)	1 (<1)
Other adverse event	51 (10)	43 (8)	36 (7)
Loss to follow-up	6 (1)	3 (<1)	7 (1)
Subject's choice	9 (2)	4 (<1)	15 (3)
Non-compliance	3 (<1)	4 (<1)	6 (1)
Non-eligibility	0	0	1 (<1)
Administrative	0	1 (<1)	0
<b>Discontinued after six months</b>	<b>31 (6)</b>	<b>36 (7)</b>	<b>42 (8)</b>
Adverse event	23 (5)	25 (5)	29 (6)
Loss to follow-up	2 (<1)	3 (<1)	6 (1)
Subject's choice	3 (<1)	6 (1)	4 (<1)
Non-compliance	3 (<1)	2 (<1)	3 (<1)

Overall 13-14% of patients discontinued therapy. The most common reasons for discontinuation of therapy were because of psychiatric, constitutional (fatigue, headache), or gastrointestinal adverse events.

Dose reduction of interferon alfa-2b was related to dose (PEG-Intron 1.5 µg/kg > PEG-Intron 0.5 µg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose reduction for ribavirin was similar across all three groups, 33-35%. The most common reasons for dose modifications were neutropenia (8-18%), and anemia (9-13%). Other reasons included depression (2-3%), fatigue (2-4%), nausea (2-4%), and thrombocytopenia (1-3%). See also analyses of ribavirin dose subgroups on **pages 34-38**. In many but not all cases, adverse events resolved after dose reduction or discontinuation of therapy. Some patients experienced ongoing or new serious adverse events during the 6-month follow-up period; 13 patients experienced life-threatening psychiatric events (suicidal ideation or attempt) and one patient accomplished suicide.

Serious adverse events

There were two deaths: one suicide in a patient receiving peginterferon/ribavirin and one death in the Interferon/ribavirin group (motor vehicle accident). The incidence of serious adverse events was 17% in the PEG-Intron/REBETOL groups and 14% in the INTRON A/REBETOL group. Three-hundred and twenty-two SAEs were reported in 172 subjects and 241 of these were reported during treatment.

The most frequently reported SAEs for all groups were listed in the following body systems (see **Table 35**).

**Table 35. Selected Serious Adverse Events by Body System**

	Body as a Whole	Psychiatric	GI	Resistance Mechanism	Vision	Respiratory	Musculo-skeletal	Endocrine
PEG 1.5	18 (4)	12 (2)	17 (3)	11 (2)	5 (1)	4 (0.8)	6 (1)	3 (0.5)
PEG 0.5	14 (3)	24 (5)	6 (1)	3 (0.6)	7 (1.4)	6 (1)	3 (0.6)	2 (0.4)
I/R	16 (3)	14 (3)	16 (3)	1 (0.2)	2 (0.4)	3 (0.6)	1 (0.2)	0

**Serious Infections:**

Nine subjects reported fifteen serious infections that were classified as resistance mechanism disorders. In the PEG 1.5/R group six subjects reported eleven infectious events. In the PEG 0.5/R group two subjects reported three infectious events. Some of the serious infections were associated with neutropenia. Other serious adverse events with presumed infectious etiology (in whole or in part) are listed under Other Body Systems in **Table 36**. The overall number of serious infections appears to be related to interferon exposure (PEG1.5 > PEG 0.5 > INF).

**Table 36. Serious Infectious Adverse Events**

	PEG 1.5/R	PEG 0.5/R	I/R
<b>Resistance Mechanism</b>			
Abscess	3	1	0
Cellulitis	5	1	1
Infection(bacterial, viral, or NOS).	3	0	0
Sepsis	0	1	0
<b>Other Body Systems</b>			
Appendicitis	4	1	0
Bronchitis	0	1	0
Pneumonia	1	1	1
Prostatitis	1	0	0
UTI	0	1	1
<b>Total</b>	<b>17</b>	<b>7</b>	<b>3</b>

**Pregnancies:**

Three study subjects became pregnant after the end of the treatment period; one of these subjects had a miscarriage and two had elective abortions. Eight partners of study subjects became pregnant during the treatment period; three of these pregnancies resulted in healthy newborns, three were terminated electively; the outcome of the other two pregnancies is unknown. Two partners of study subjects became pregnant in the post-treatment follow-up period; both pregnancies were terminated electively.

**Listing of Serious Adverse Events:**

Individual serious adverse events occurred at a frequency  $\leq 1\%$ . The events included suicide attempt, suicidal ideation, severe depression; psychosis, agitation,

aggressive reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia, retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema, bronchiolitis obliterans, pleural effusion, gastroenteritis, pancreatitis, gout, weight decrease, fatigue, fever, diabetes mellitus, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis, vasculitis, phototoxicity. See Clinical Narrative Section for summaries of selected serious adverse events.

Eighty-one serious adverse events were reported during the six-month follow up period. The incidence was around 5% across treatment groups.

#### Life-threatening and severe adverse events

The incidence of life-threatening adverse events was  $\leq 1\%$  across all groups. The incidence of severe adverse events was 31-34% in the PEG-Intron/REBETOL groups and 23% in the INTRON A/REBETOL group.

#### Most common adverse events

Nearly all study patients experienced one or more adverse events. The most common adverse events were psychiatric and occurred among 77% of patients. The most common individual psychiatric events were depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up after treatment cessation (see **Table 37**).

PEG-Intron induced fatigue or headache in approximately two-thirds of patients, and induced fever or rigors in approximately half of the patients. The severity of some of these systemic symptoms (e.g. fever and headache) tended to decrease as treatment continued. The incidence tended to be higher with PEG-Intron than with Intron A therapy alone or in combination with REBETOL.

Application site inflammation and reaction (e.g. bruise, itchiness, irritation) occurred at approximately twice the incidence with PEG-Intron therapies (in up to 75% of patients) compared with INTRON A. However injection site pain was infrequent (2-3%) in all groups. Other common adverse events in the PEG-Intron/REBETOL group included myalgia (56%), arthralgia (34%), nausea (43%), anorexia (32%), weight loss (29%), alopecia (36%), and pruritus (29%).

**Table 37. Adverse Events Occurring in > 5% of Patients**

<b>Adverse Events</b>	<b>PEG 1.5/R</b>	<b>I/R</b>
<b>Application Site</b>		
Injection Site Inflammation/Reaction	75	49
<b>Autonomic Nervous System</b>		
Mouth Dry	12	8
Sweating Increased	11	7
Flushing	4	3
<b>Body as a Whole</b>		
Fatigue/Asthenia	66	63
Headache	62	58
Rigors	48	41
Fever	46	33
Weight Decrease	29	20
RUQ Pain	12	6
Chest Pain	8	7
Malaise	4	6
<b>Central/Peripheral Nervous System</b>		
Dizziness	21	17
<b>Endocrine</b>		
Hypothyroidism	5	4
<b>Gastrointestinal</b>		
Nausea	43	33
Anorexia	32	27
Diarrhea	22	17
Vomiting	14	12
Abdominal Pain	13	13
Dyspepsia	9	8
Constipation	5	5
<b>Hematologic Disorders</b>		
Neutropenia	26	14
Anemia	12	17
Leukopenia	6	5
Thrombocytopenia	5	2
<b>Liver and Biliary System</b>		
Hepatomegaly	4	4
<b>Musculoskeletal</b>		
Myalgia	56	50
Arthralgia	34	28
Musculoskeletal Pain	21	19
<b>Psychiatric</b>		
Insomnia	40	41
Depression	31	34
Anxiety/Emotional Lability/Irritability	47	47

<b>Adverse Events</b>	<b>PEG 1.5/R</b>	<b>I/R</b>
Concentration Impaired	17	21
Agitation	8	5
Nervousness	6	6
<b>Reproductive, Female</b>		
Menstrual Disorder	7	6
<b>Resistance Mechanism</b>		
Infection Viral	12	12
Infection Fungal	6	1
<b>Respiratory System</b>		
Dyspnea	26	24
Coughing	23	16
Pharyngitis	12	13
Rhinitis	8	6
Sinusitis	6	5
<b>Skin and Appendages</b>		
Alopecia	36	32
Pruritus	29	28
Rash	24	23
Skin Dry	24	23
<b>Special Senses Other,</b>		
Taste Perversion	9	4
<b>Vision Disorders</b>		
Vision blurred	5	6
Conjunctivitis	4	5

\*Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

### Laboratory Values

#### **Hemoglobin**

REBETOL induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to <11g/dl in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-Intron/REBETOL and INTRON A /REBETOL groups. Hemoglobin levels become stable by treatment week 4-6 on average. Hemoglobin levels return to baseline between 4 and 12 weeks post-treatment.

#### **Neutrophils**

Decreases in neutrophil counts were observed in a majority of patients treated with PEG-Intron alone (70%) or as combination therapy with REBETOL (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia (<0.5 x 10<sup>9</sup>/L) occurred in 1% of patients treated with PEG-Intron monotherapy, 2% of patients treated with INTRON A/REBETOL and in 4% of patients treated with PEG-Intron/REBETOL. Two percent of patients receiving PEG-Intron monotherapy and 18% of patients receiving PEG-Intron /REBETOL required modification of

interferon dosage. Few patients ( $\leq 1\%$ ) required permanent discontinuation of treatment. Neutrophil counts generally return to pre-treatment levels within 4 weeks of cessation of therapy.

### ***Platelets***

Platelet counts decrease in approximately 20% of patients treated with PEG-Intron alone or with REBETOL and in 6% of patients treated with INTRON A/REBETOL. Severe decreases in platelet counts ( $<50,000/\text{mm}^3$ ) occur in  $<1\%$  of patients. One to three percent of patients required dose modification of INTRON A or PEG-Intron respectively. Platelet counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

### ***Thyroid Function***

Development of TSH abnormalities, with and without clinical manifestations, is associated with interferon therapies. Clinically apparent thyroid disorders occur among patients treated with either Intron A or PEG-Intron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). 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.

### ***Bilirubin and Uric acid***

In the present study 10-14 % of patients developed hyperbilirubinemia and 33-38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

## **SELECTED CLINICAL NARRATIVES OF SERIOUS ADVERSE EVENTS**

Brief summaries of serious adverse events are provided to illustrate some of the syndromes associated with the study treatments. The cases were selected based on their clinical significance, the adequacy of documentation and the treatment group (preference was given to the Peg 1.5/R arm).

For the narratives please see **APPENDIX 3**.

## **OTHER SAFETY DATA**

### **Immunogenicity**

Approximately 2% of patients receiving PEG-Intron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer ( $\leq 160$ ) neutralizing antibodies to PEG-Intron or INTRON A. No apparent correlation of antibody development to clinical response or adverse events was observed. The incidence of post-treatment binding antibody ranged from 8 to 15 percent.

### **Overdosage**

A few patients accidentally received a dose greater than that prescribed. There were no instances in which a patient received more than 10.5 times the intended dose of PEG-Intron. The maximum dose received by any patient was 3.45  $\mu\text{g}/\text{kg}$

weekly over a period of approximately 12 weeks. There were no significant ribavirin overdosages in this study; the maximum known overdosage of ribavirin was an intentional ingestion of 10 g (fifty 200 mg capsules). There were no serious reactions attributed to these overdosages.

#### Concomitant medications

There was a major increase in the use of psychotherapeutics, analgesic and anti-inflammatory during the course of the treatment period consistent with the incidence of psychiatric, systemic and musculoskeletal adverse events. Use of antimicrobials, antihistaminics and dermatologic drugs also increased. There was no difference between study arms in concomitant medication usage (see **Table 38**).

**Table 38. Concomitant Medication Usage**

Medication class	PEG 1.5/R		PEG 0.5/R		I/R	
	Baseline	Treatm.	Baseline	Treatm.	Baseline	Treatm.
Analgesic	81 (16)	411 (80)	89 (17)	399 (78)	91 (18)	397 (79)
Antidiarrhea, GI antiinfective	0	40 (8)	3 (1)	15 (3)	2 (<1)	29 (6)
Antiemetic, antinauseant	0	22 (4)	2 (<1)	29 (6)	0	22 (4)
Antiinflammatory/antirheum.	59 (12)	237 (46)	58 (11)	230 (45)	56 (11)	216 (43)
Corticosteroids, dermatologic	8 (2)	88 (17)	10 (2)	77 (15)	8 (2)	84 (17)
Psychoanaleptic	65 (13)	204 (40)	57 (11)	188 (37)	69 (14)	179 (35)
Psycholeptic	37 (7)	119 (23)	35 (7)	150 (29)	44 (9)	127 (25)
Systemic antibiotics	28 (5)	142 (28)	15 (3)	130 (25)	21 (4)	124 (25)
Systemic antihistamines	31 (6)	126 (25)	23 (4)	134 (26)	16 (3)	121 (24)

#### Adverse event reporting by geographic region

The table below shows a selected list of adverse events by geographic region in patients treated with PEG 1.5/R and I/R. Study centers in the US reported a higher number of adverse events compared to study centers from other countries.

**Table 39. Selected Adverse Event Reports from US and Non-US Study Centers**

Adverse event	PEG 1.5/R		I/R	
	US	Non-US	US	Non-US
Myalgia	241 (70) <sup>1</sup>	67 (40)	197 (58)	64 (38)
Injection site reaction	208 (61)	91 (54)	116 (34)	68 (40)
Headache	237 (70)	90 (54)	216 (63)	94 (56)
Rigors	195 (57)	52 (31)	159 (47)	49 (29)
Nausea	181 (53)	44 (26)	142 (42)	40 (24)
Fever	175 (51)	67 (40)	107 (31)	61 (36)
Insomnia	168 (49)	51 (30)	171 (50)	56 (33)
Arthralgia	155 (45)	54 (32)	138 (40)	40 (24)
Depression	131 (38)	53 (32)	135 (40)	48 (29)
Irritability	140 (41)	41 (24)	134 (39)	40 (24)

Alopecia	134 (39)	54 (32)	111 (33)	51 (30)
Anorexia	127 (37)	42 (25)	101 (30)	38 (23)
Weight decrease	92 (27)	61 (36)	64 (19)	46 (27)
Neutropenia	100 (29)	34 (20)	49 (14)	20 (12)
Anemia	46 (13)	16 (10)	58 (17)	26 (15)

<sup>†</sup> Numbers in parentheses are percentages

Weight decrease and asthenia were the only two adverse events with higher reporting rates by non-US centers.

The reporting rate for asthenia was higher in non-US centers (40% vs. 10%) compared to the rate in the US centers. The reporting rate for fatigue was lower in non-US centers (50 vs. 85%). These differences are likely due to regional differences in the use of the terms asthenia or fatigue to describe the same symptom.

Regional differences in the rate of reports were observed for both symptomatic (e.g. myalgia, anorexia) and quantifiable (e. g. neutropenia, alopecia) events. The cause of these differences was not further assessed. Non-drug related causes (e.g. differences in ascertainment procedures by investigators or in spontaneous reporting by patients) may account partly or fully for the difference between regions in the number of all adverse events.

The numbers of serious adverse events were too few for the purpose of this subgroups analysis; no consistent numerical differences between regions were observed.

#### Carcinogenic potential of ribavirin

Ribavirin is genotoxic and mutagenic. No data are available on the carcinogenic potential of ribavirin.

#### *Reviewer's comment*

*The package insert should contain a warning indicating that ribavirin is a potential carcinogen. The sponsor should provide timelines for the completion and reporting to CBER ongoing preclinical studies to address this question.*

#### Embryocidal and teratogenic activity of ribavirin

This supplement does not contain new information on these risks.

#### *Reviewer's comment*

*The package insert should contain a warning about these risks and should instruct patients on the need for adequate contraception.*

## SUMMARY AND DISCUSSION

### EFFICACY OF PEGINTERFERON ALFA-2B AND RIBAVIRIN

Primary efficacy outcome: Loss of detection of HCV RNA in serum at end of follow up period.

- The response to treatment with 1.5 µg/kg peginterferon-alfa 2b and 800 mg ribavirin (52%) is superior to the response to treatment with  $3 \times 10^6$  Units interferon alfa-2b and 1000 –1200 mg ribavirin (46%). The treatment difference is modest (difference is 6%, 95% C.I. 0.18%, 11.6%).
- The response to treatment with peginterferon alfa-2b (1.5µg/kg for 4 weeks then 0.5 µg/kg for 44 weeks ) plus ribavirin 1000-1200 mg is not superior to the response to treatment with interferon plus ribavirin.
- In the peginterferon monotherapy study the 1.5 µg/kg dose was not superior in efficacy to the 1.0 µg/kg dose and had higher toxicity. Given these observations, the safety and efficacy of combination treatment with peginterferon 1.5 µg/kg plus ribavirin should be compared to that of peginterferon 1.0 µg/kg plus ribavirin.
- The proportion of patients who relapse after the end of the treatment was highest in the PEG 1.5/R group.
- The proportion of treatment responders who achieve loss of HCV RNA is around 90-95% by treatment week 12 and 99% by week 24. The package insert should recommend treatment discontinuation in patients with persistent high viral titers at 6 months of treatment.
- HCV genotype 1, high levels of circulating HCV RNA ( $>2 \times 10^6$  copies/ml serum), and presence of advanced liver fibrosis are associated with less favorable response to treatment.
- Treatment responses are higher in patients with genotypes 2 and 3 and time to first response is shorter ( $\leq 3$  months) in these patients. Treatment responses are also higher in patients with low viral load ( $< 2 \times 10^6$ /ml plasma). Treatment regimens of shorter duration (e.g. six months) should be evaluated in these patients.
- In general, younger patients appeared to have higher response rates than older patients. No pediatric studies of peginterferon and ribavirin have been performed. Treatment responses appeared to be higher in women.

- Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied was insufficient to allow meaningful conclusions about differences in response rates. The prevalence of HCV in the US is higher in African Americans and in Hispanics compared to Caucasians, and these two ethnic minorities were under-represented in the study. Treatment responses should be studied further in these minorities.
- Differences in response rates between treatment arms varied somewhat with body weight. Patients with lower body weight tended to have higher response rates than patients with higher body weights. A number of factors could account for this apparent interaction between body weight and treatment response. From the data and the analyses performed by the sponsor it could not be determined if patients with lower body weight had higher response rates because of higher exposures to ribavirin.
- No data are available about responses in patients who have failed previous interferon alfa-2b treatment.

#### Secondary efficacy outcomes

##### Biochemical Response at End of Follow up Period.

The estimate of treatment response using normalization of serum ALT was generally consistent with the estimate using loss of detection of HCV RNA in serum.

##### Biochemical Response at End of Treatment Period.

The proportion of patients with normalization of serum ALT at the end of the treatment period was not higher in the peginterferon-treated groups.

##### Virologic Response at End of Treatment Period.

The proportion of patients with loss of detection of HCV RNA at the end of the treatment period was higher in the PEG1.5/R arm compared to the I/R arm.

##### Scores for Liver Inflammation and Fibrosis.

Scores for hepatic inflammation and fibrosis were not superior with peginterferon and ribavirin treatment compared to interferon and ribavirin.

##### Health-Related Quality of Life Scores.

The QOL scores were not improved in any of the treatment groups either during or after treatment.

### Effect of food on ribavirin absorption

Ribavirin should be taken with food. Additional studies to better characterize the food effects should be performed

### **SAFETY OF PEGINTERFERON ALFA-2B AND RIBAVIRIN**

- Patients receiving PEG-Intron 1.5 µg/kg and ribavirin required dose modification more frequently compared to patients receiving interferon and ribavirin. In many but not all cases, adverse events resolved after dose reduction or discontinuation of therapy.
- The incidence of serious adverse events and of severe adverse events was numerically somewhat higher in the PEG 1.5/R arm compared to I/R.
- The overall number of serious infections appears to be related to interferon exposure (PEG 1.5 > PEG 0.5 > INF). In some patients serious infections were associated with neutropenia. The incidence of severe neutropenia (4% vs. 2%), and dose reduction (18% vs. 8%) and discontinuations (1% vs. 0.2%) for neutropenia were higher in the PEG 1.5/R group compared to the I/R group.
- Some patients experienced ongoing or new serious adverse events during the 6-month follow-up period; 13 patients experienced life-threatening psychiatric events (suicidal ideation or attempt) and one patient accomplished suicide.
- Psychiatric events occurred in 77% of patients. The most common individual psychiatric events were depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up. Note: insomnia can be associated with psychiatric event, but is sometimes classified differently.
- Fatigue or headache was observed in approximately two-thirds of patients, and fever or rigors in approximately half of the patients. The severity of some of these systemic symptoms (e.g. fever and headache) tended to decrease as treatment continued. The incidence tended to be higher with PEG-Intron and ribavirin compared to Intron A and ribavirin.
- Application site inflammation and reaction (e.g. bruise, itchiness, irritation) occurred at approximately twice the incidence with PEG-Intron therapies (in up to 75% of patients) compared with INTRON A. However injection site pain was infrequent (2-3%) in all groups. Other common adverse events in the PEG-Intron/REBETOL group included

myalgia (56%), arthralgia (34%) nausea (43%), anorexia (32%), weight loss (29%), alopecia (36%), and pruritus (29%).

- Hemoglobin levels decreased to <11g/dl in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Hemoglobin levels become stable by treatment week 4-6 on average. Hemoglobin levels return to baseline between 4 and 12 weeks post- treatment.
- Decreases in neutrophil counts were observed in a majority of patients treated with PEG-Intron with REBETOL (85%) and INTRON A/REBETOL (60%). Neutrophil counts generally return to pre-treatment levels within 4 weeks of cessation of therapy.
- Platelet counts decrease in approximately 20% of patients treated with PEG-Intron with REBETOL and in 6% of patients treated with INTRON A/REBETOL. Severe decreases in platelet counts (<50,000/mm<sup>3</sup>) occur in <1% of patients. One to three percent of patients required dose modification of INTRON A or PEG-Intron respectively. Platelet counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.
- Development of TSH abnormalities, with and without clinical manifestations, is associated with interferon therapies. Clinically apparent thyroid disorders occur among patients treated with either Intron A or PEG-Intron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). 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.
- Ribavirin is known to have mutagenic, genotoxic, embryocidal, and teratogenic effects. Warnings about potential carcinogenicity, and about risks of birth defects or death of the fetus should be mentioned in the package insert.
- In view of the dose-dependent toxicities of ribavirin more studies are needed to optimize the ribavirin dose. Patients with lower than average body weight should be followed carefully for interferon and ribavirin-induced toxicities.

#### **COMPARISON OF ACTIVITY AND SAFETY OF WEIGHT-BASED RIBAVIRIN ACROSS STUDY ARMS**

The comparison of treatment response based on ribavirin weight-adjusted dose is a post-hoc analysis.

Due to differences in dosing regimens (see below), sorting data by ribavirin dose (mg/kg) results in subgroups that are different in numbers, body weights, and may differ in other unknown factors.

	PEG 1.5 $\mu\text{g}/\text{kg}/\text{wk}$ R 800 mg/qd	PEG 0.5 $\mu\text{g}/\text{kg}/\text{wk}$ R 1000-1200mg/qd	IFN $9 \times 10^6$ U/wk R 1000-1200 mg/qd
Interferon	Weight adjusted	Weight adjusted	No weight adjustment
Ribavirin	"Lower" dose. No weight adjustment	"Higher" dose. Crude weight adjustment	"Higher" dose. Crude weight adjustment

There is a modest effect of body weight on treatment response that is not consistent across study arms and subgroups.

There is an effect of body weight on adverse events (both ribavirin- and interferon-associated) and on the incidence of dose-reduction due to adverse events. There is a suggestion of threshold where steeper increase in ribavirin toxicity may be seen.

Multiple other factors affect response to treatment. In multivariate regression analyses weight makes a small contribution to the model.

There are insufficient US data on safety/activity of higher exposure to ribavirin in the PEG1.5 group and also in other dose groups due to study design and to higher than expected body weights of study subjects (US mean 85 kg; ribavirin dose adjustment 1000 vs. 1200mg based on 75kg).

The sponsor's analyses of safety and activity data in original submission were incomplete. The sponsor's proposed weight-based scheme raised safety concerns due to high exposure of patients in certain weight subgroups.

Studies are ongoing to compare safety and efficacy of weight-based and fixed-weight ribavirin.

## CONCLUSIONS

The response to treatment with 1.5  $\mu\text{g}/\text{kg}$  peginterferon-alfa 2b and 800 mg ribavirin is superior to the response to treatment with  $3 \times 10^6$  Units interferon alfa-2b and 1000 –1200 mg ribavirin. The treatment difference is modest.

A number of serious toxicities are associated with interferon and ribavirin treatment.

Dose-modification or discontinuation for hematologic, psychiatric, autoimmune and other adverse events is frequently necessary. Serious adverse events frequently but not always reverse with discontinuation of treatment. Regular clinical and

laboratory assessment of patients and patient education are essential to prevent or mitigate serious adverse reactions.

The risk benefit of peginterferon 1.5 µg/kg and ribavirin 800 mg in patients with chronic hepatitis C is acceptable.

The overall risk/benefit of ribavirin doses higher than 800 mg daily is not known. There is evidence of higher toxicity associated with higher ribavirin dosage without compelling data on known clinical benefits.

There is no definitive evidence that interferon treatment of chronic hepatitis C decreases the incidence of serious long-term outcomes such as cirrhosis or hepatocellular carcinoma. Given these considerations, antiviral treatment should be reserved for patients with documented HCV-induced liver damage (i.e. detectable HCV RNA, elevated serum ALT, histologic evidence of liver fibrosis and inflammation). The liver disease should be compensated.

Additional studies are needed in the post-marketing phase to explore:

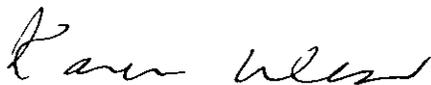
- The optimum dose of ribavirin to determine if a higher doses (administered on basis of body weight) can achieve higher response rates without higher risk of serious irreversibly toxicity.
- The optimum dose of peginterferon to determine if a lower dose (1.0 µg/kg) can achieve a similar response rate without the higher risk associated with the 1.5 µg/kg dose.
- The optimum duration of peginterferon and ribavirin treatment in patients with high likelihood of response such as patients with HCV genotype 2-3, and genotype 1 with low viral load. The aim is to determine if shorter duration of treatment (e.g. 6 months) can achieve similar response rates while avoiding the added toxicity of longer treatment.
- The effects of food on single-dose ribavirin absorption (e.g. effects of high fat vs. high non-fat caloric intake) and achievement of steady state after multiple dosing of ribavirin.

#### **RECOMMENDED REGULATORY ACTION**

Peginterferon alfa-2b and ribavirin has been shown to be safe and effective for the treatment of patients 18 years of age and older with compensated chronic hepatitis C who have not been previously treated with interferon alpha. Approval is recommended.



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



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

## APPENDIX 1

### **ADMINISTRATIVE ISSUES**

#### Priority review

The sponsor requested priority review of the application because the sponsor believes that the benefits of peginterferon/ribavirin therapy meet the criteria of expedited review i.e. that the therapy meets a serious and unmet medical need. This is based mostly on the observation that clinical data show that the proportion of responders to peginterferon/ribavirin treatment is higher than the proportion of responders to interferon/ribavirin. The sponsor also believes, without supporting data, that the once weekly dosing of peginterferon (compared to thrice weekly dosing with interferon) may increase patient compliance to the combination treatment.

Given the seriousness of complications associated with chronic hepatitis C infection and the postulated improved efficacy of peginterferon/ribavirin compared to other available antiviral therapies, the agency granted the priority review.

#### Licensing status of drug product

At the time this application was submitted, peginterferon plus ribavirin was not licensed in any country, nor had it been withdrawn from marketing in any country. A number of license applications for peginterferon plus ribavirin for the treatment of chronic hepatitis C were pending. Since the time of the submission the EU health authorities approved peginterferon and ribavirin combination therapy in patients with chronic hepatitis C for marketing in the EU.

#### Disclosure of financial interests and arrangements of clinical investigators

The following is a listing of investigators who disclosed that they, their spouses and dependent children received payment of other sorts from Schering Plough on or after February 2, 1999.

<u>In excess of \$25,000</u>	<u>In excess of \$ 50,000</u>
	
	

The sponsor believes that the assessment of the efficacy endpoint by a centralized laboratory and design features of the study (including randomization, participation of multiple clinical centers, control group) minimized investigator bias.

#### *Reviewer's comments*

*The randomization period of the phase 3 study began in January 1999 and recruitment and negotiations with study sites would have begun even earlier. The*

*reviewer asked the sponsor to provide information on payments to investigators from after January 1, 1998 to cover the time period before the study when the investigators were recruited for participation in the study. The sponsor reviewed his records and found no additional relevant information.*

#### Debarment certification

None of the clinical investigators participating in the study have been debarred under section 306 of the FDC act.

#### Statement of compliance

The sponsor states that the clinical trials were conducted in accordance with good clinical practice. All the US investigators agreed to comply with federal regulations (21 CFR part 50) concerning informed consent and human subject protection. All the investigators outside the US agreed to comply with the declaration of Helsinki. For the phase 3 study only, the international investigators also agreed to comply with US regulations. IRBs or ethical committees reviewed the clinical protocols.

#### Transfer of regulatory obligations

For the phase 3 study the sponsor transferred to four CROs (L, J, K, and M) the following monitoring responsibilities for all the US study centers (protocol C98-580): monitoring visits, review of patient charts, drug accountability, review of regulatory documents, data clean up, entry of liver biopsy information in the database.

L (a CRO) performed the central randomization for both the US and International portions of the phase 3 study and contributed to packaging and shipment of drug supplies.

#### **DATA AUDITS**

The sponsor verified a number of variables between Case Report Form entries and source documents for a representative sample of subjects.

#### Remote data entry

Data were acquired through remote data entry. The data were checked during the data entry process for completeness and out-of-range values discrepancies identified were corrected during the data entry process.

The data were sent to the sponsor via modem and uploaded into a Clintrial database. A program that included range checks and checks for completeness and logical errors was used to check data. The sponsor performed a complete check of adverse event, dose, virology, death, demographic, treatment status and follow-up status data on 5% (76) of the patients and found no errors.

All central laboratory data were obtained by electronic transmission from L, J, K, and M and were loaded into the SAS reporting database.

Verification of efficacy data

A central laboratory [redacted] performed the virologic assays. The laboratory was not required to generate and send to the sponsor a hard copy of the virologic data. The primary source document for these data is the electronic transmission from [redacted] that was uploaded into the SAS reporting database used by the sponsor. The study protocol did not describe the procedure for reporting virology data to the investigators and did not specify when patients were to be informed of the results. The virology data were not captured in the case report form.

*Reviewer's comment*

*The BLA contained no validation of the process for capturing the primary efficacy variable namely HCV RNA and the covariates used in the primary efficacy analysis (HCV genotype and presence of cirrhosis at baseline).*

*The central virology laboratory was asked to provide a hard copy of HCV RNA titers and genotype for all study patients. The reviewer used this document to verify the viral data in line listings and CRTs of the BLA. As an additional check the sponsor ran a validation test of the electronic data transfer process and provided the documentation to the BLA file.*

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## APPENDIX 2

### ONGOING CLINICAL STUDIES

#### Studies of peginterferon in patients with malignancies or HCV/HIV co-infection

The following INDs provided additional safety data reviewed for this license application. The sponsor (Schering Plough) holds IND 7572 for PEG-Intron and ribavirin for the treatment of chronic hepatitis C. The sponsor is also evaluating PEG-Intron as monotherapy in patients with chronic hepatitis C (IND — ), neoplastic disease (IND — ), multiple sclerosis (IND — ), and HIV (IND — ). In addition there are a number of sponsor-investigator INDs for the study of peginterferon and ribavirin in patients with chronic hepatitis C. Finally there are a number of investigator-sponsored studies of PEG Intron monotherapy for non-hepatitis indications (see **Table 1**).

**Table 1. Investigator-Sponsored INDs for Peginterferon in Other Indications**

INVESTIGATOR	IND NUMBER AND TITLE
Bukowski, Ronald, MD Cleveland Clinic Foundation	IND — "A Phase I Trial of PEG-Intron and IL-2 in Patients with Metastatic Renal Cell Carcinoma"
Clark, Joseph, MD Loyola University	IND — "A Phase I/II Trial of Outpatient PEG-Intron with IL-2 in Advanced Renal Cell Carcinoma"
Division of AIDS, NIAID	IND # not yet assigned "A5088 Pilot Study of Low Dose Interleukin-2 and Pegylated Interferon and Ribavirin for the Treatment of Hepatitis C Infection in Subjects with HIV Co-Infection"
Division of AIDS, NIAID	IND — "PACTG 1017 Safety, Tolerability, Antiviral Activity and Pharmacokinetics of PEG-Intron in HIV-Infected Children"
	IND — "Phase II Study of SCH 54031 (PEG Interferon Alfa-2B/PEG-Intron) in Patients with Essential Thrombocythemia, Polycythemia Rubra Vera and Myelofibrosis"
Herbst, Roy, MD MD Anderson Cancer Center	IND — "A Phase II Study of SCH54031 (Peg Interferon Alfa-2B/PEG-Intron) in Recurrent Squamous Cell Tumors of the Head and Neck"
	IND — "A Phase II Study of SCH 54031 (PEG Interferon Alfa-2B/PEG Intron) in Subjects with Interferon-Refractory Chronic Myelogenous Leukemia" "Therapy of Early Chronic Phase Chronic Myelogenous Leukemia (CML) with SCH 54031 (PEG Interferon Alpha 2b) and Low-Dose Cytosine Arabinoside (ARA-C)"
	IND — "Phase II Study of Weekly Administered High Dose Pegylated Interferon Alpha-2b (PEG-Intron) in Advanced Stage Low Grade Non Hodgkins Lymphoma"
	IND — "Phase I/II of Autologous CD34-Selected Peripheral Cells Transplantation with Thalidomide and PEG-Intron Maintenance as Treatment for Multiple Myeloma"

#### *Reviewer's comments*

*For this review, serious and unexpected adverse event data from non-HCV studies were obtained from IND safety reports (mainly as cross-references to IND 7572) and from the interim safety update to this BLA supplement. In most cases the underlying disease (e.g. neoplastic disease, HIV infection, MS) and concomitant medications was judged to play a role in the adverse events. The following safety reports provided new or supportive data for the following syndromes: mania/bipolar disorder (N=3), injection site necrosis (N=2), mucosal and/or skin inflammation (Stevens-Johnson syndrome N=2, and erythema multiforme, N=1), ARDS, interstitial pneumonia (N=2), fatal hepatorenal syndrome (in a patient with*

compensated cirrhosis at study entry), bone marrow toxicity (N=2). For discussion of these serious adverse events see the Clinical Narrative section.

Lactic acidosis appeared to be associated with peginterferon/ribavirin. However the acidosis was observed exclusively in patients with HIV/HCV co-infection and was associated (in all but one case) with concomitant antiretroviral drugs. Notably the patient with HIV who developed lactic acidosis in the absence of antiretroviral drugs had a positive de-challenge and re-challenge to peginterferon/ribavirin.

Ongoing studies of peginterferon in patients with hepatitis C

The table below lists two ongoing studies that aim to address important unresolved questions in studies of patients with HCV. The first is a study comparing fixed-dose to weight-based ribavirin; the other is a study to better characterize treatment responses in African Americans.

**Table 2. Investigator-sponsored INDs of Peginterferon and Ribavirin in Patients with HCV**

INVESTIGATOR	IND NUMBER AND TITLE
C J	IND — A Research Study of Pegylated Interferon alfa 2b and ribavirin for the treatment of hepatitis C in African Americans and Caucasians
C J	IND — Comparison of PEG Interferon alfa-2b plus Ribavirin Given as a Fixed Dose or on a Weight Optimized Basis for Treatment of Chronic Hepatitis C in Previously Untreated Adult Subjects

Numerous other ongoing investigator-sponsored studies aim to evaluate treatment regimens for patients who failed to respond or relapsed after previous interferon-based therapies. Approaches include changes in drug doses and schedules, induction treatment or long-term maintenance treatment, and additional experimental treatments. No data are available from any of these studies.

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## APPENDIX 3

### STUDIES OF INTERFERON/RIBAVIRIN TREATMENT IN PEDIATRIC PATIENTS WITH CHRONIC HEPATITIS C

#### INTRODUCTION

In pediatric patients currently the main routes of hepatitis C virus (HCV) infection are vertical transmission and sporadic infection. In the US around 50% of children infected with HCV develop chronic hepatitis. After several years, liver cirrhosis develops in about 20% of adults with chronic HCV infection. In children with chronic HCV the incidence of cirrhosis is lower compared to adults due to shorter duration of infection and possibly slower rate of progression of disease.

Around 40-45% of adults treated for 1 year with interferon alfa-2b ( $3 \times 10^6$  TIW, SC) plus ribavirin (1000-1200 mg daily PO) achieve loss of detectable HCV RNA at 6 months after the end of treatment. This response rate was judged to be sufficient to justify the study of interferon plus ribavirin in children with chronic HCV hepatitis.

#### CLINICAL STUDIES

IFN ( $3 \text{ MIU/m}^2$  TIW) showed antiviral activity in 12 children with chronic HCV hepatitis. IFN ( $6 \text{ MIU/m}^2$  TIW for 24 weeks) showed acceptable safety and activity in 72 pediatric patients with chronic hepatitis B.

**Table 1. Pediatric Studies of Interferon alfa-2b plus Ribavirin in Chronic HCV**

Protocol (N)	Study Design	Study Treatment
<u>C</u> <u>1</u> Part 1 (N=61)	Open-label uncontrolled, randomized, dose ranging.	IFN ( $3 \times 10^6$ U/m <sup>2</sup> SC TIW) plus ribavirin (8, 12, or 15 mg/kg/day PO) for 48 weeks; 24-week follow-up.
Part 2 (N=35)	Open-label, single arm	IFN ( $3 \times 10^6$ U/m <sup>2</sup> SC TIW) plus ribavirin (15 mg/kg/day PO) for 48 weeks; 24-week follow-up.
<u>—</u> (N=70)	Open-label, single arm, multi-center, fixed dose.	IFN ( $3 \times 10^6$ U/m <sup>2</sup> SC TIW) plus ribavirin 15 mg/kg/day PO for 48 weeks; 24-week follow-up.

#### Protocol C 1

The objective of part 1 was to select a dose of ribavirin for further study based on pharmacokinetic and pharmacodynamic assessments during the treatment period. By endpoint (treatment week 12), mean decreases in serum HCV-RNA levels ranged from -2.5 to -3.0 log in the three dose groups. The 15 mg/kg/day ribavirin dose achieved the highest mean reduction in HCV-RNA levels and was chosen for study in part 2. The objective of part 2 was to assess PK and clinical activity of the IFN/ribavirin-15 mg/kg/day treatment selected in part 1.

## Protocol —

The objective of this protocol was to evaluate the efficacy of IFN ( $3 \times 10^6$  U/m<sup>2</sup> SC TIW) plus ribavirin 15 mg/kg/day PO for 48 weeks; 24-week follow-up.

## COMBINED SUMMARY OF PROTOCOL [ ]

Twenty patients in — part 1, thirty-five patients in — part 2 and seventy patients in — were to receive IFN ( $3 \times 10^6$  U/m<sup>2</sup> SC TIW) plus ribavirin 15 mg/kg/day PO for 48 weeks. The efficacy and safety data from these 125 patients was pooled.

### Enrollment criteria

Patients had to meet the following requirements.

- Age between 3 and 16 years.
- Diagnosis of chronic HCV hepatitis made by liver biopsy and HCV-RNA.
- Hematologic and biochemical measurements within acceptable ranges.
- Absence of cirrhosis.
- Treatment-naïve/treatment -failure [ ] or treatment-naïve [ ] ( ).

### Patient demographics

The 125 study patients had a median age of 11 years and a median body weight of 40 kg; 80% of the subjects were Caucasian in origin. Table 002 summarizes selected demographic characteristics of study patients.

Table 2. Combined Data [ ] Demographics

Age range		Weight range		Gender		Ethnic origin	
Years	N	Kg	N		N		N
3-6	21 (17)	<46	77 (62)	Female	56 (45)	Caucasian	101 (81)
7-9	26 (21)	>46 -55	14 (11)	Male	69 (55)	Non-Cauc.	24 (19)
10-12	32 (26)	> 55	34 (27)	--	--	--	--
13-15	33 (26)	--	--	--	--	--	--
15-16	13 (10)	--	--	--	--	--	--

Numbers in parentheses are percentages

Table 3 shows the principal characteristics of HCV infection in the study patients at baseline. Nearly 80% of patients were infected with HCV genotype 1 and 54% of patients had high ( $>2 \times 10^6$  copies/ml) circulating levels of HCV RNA. The prevalence of the two unfavorable prognostic criteria is comparable with the prevalence in studies of adults conducted by the sponsor.

Table 3. Combined Data [ ] Disease Characteristics

HCV Genotype		HCV-RNA (copies/ml)		Source of Infection		Duration of Infection	
1	97 (78)	≤2 million	58 (46)	Transfusion	42 (34)	Minimum	1
2,3, or 4	28 (22)	>2 million	67 (54)	Vertical	66 (53)	Maximum	17
				Sporadic	6 (5)		

Numbers in parentheses are percentages

### IFN exposure of children

Children received more INTRON A per unit of body surface area compared to adults. The 3MIU/m<sup>2</sup> dose in pediatric patients may be compared to the 3MIU/1.6m<sup>2</sup> in the average adult. Thus the exposure is 1.6 X greater in children compared to adults.

### Efficacy outcome

There is no efficacy data in the other 105 patients. As of November 1, 2000, over 90% of patients in Part 2 and in — had received 24 weeks of treatment; <10% had received 48 weeks of treatment.

### Safety outcomes

In these ongoing studies, at least 95% of patients have been treated for 12 weeks, with the majority completing 24 weeks.

### Adverse Events

There were no deaths. There were three life-threatening/potentially life-threatening adverse events: a suicide attempt, another severe depression and a severe neutropenia. Serious adverse events were reported in 7 children: suicide attempt, suicidal ideation, depression, post-operative infection, dehydration, diabetes mellitus, vomiting, and diarrhea. Severe adverse events were reported in 18% (22/125) of children and included: depression, irritability, insomnia, somnolence, injection site reaction, fatigue, headache, flu-like symptoms, anorexia, diarrhea, and musculoskeletal pain.

The most common adverse events were fatigue, fever and headache and each was reported in two thirds of children. Anorexia, vomiting, and abdominal pain were reported in 40-50% of children. One fourth of children lost weight. Psychiatric adverse events were reported in about half of the children and included depression, emotional lability, irritability, agitation, insomnia, somnolence. Musculoskeletal pain was reported in about half of the children.

Among the 166 children treated in the current pediatric trials there have been 3 reports of suicidal ideation, and 1 report of attempted suicide, to date Three of the 4 patients who had suicidal ideation or an attempt were adolescents.

### Dose modifications or discontinuation for adverse events

Dose modifications were 18% (22/125) for interferon, 6% (7/125) for rebetol and 7%(9/125) for both drugs combined. The most common reasons for dose modification were anemia, neutropenia, fatigue, headache, and nausea and vomiting. Dose modification for psychiatric adverse events was 5%.

Seven patients discontinued treatment for the following reasons: suicide attempt, severe depression, severe neutropenia, malaise, injection site pain, and headache.

#### Clinical Laboratory Evaluation

Decreases in RBC, neutrophil, and platelets were commonly observed. Hemoglobin levels to <10 g/dL occurred in nine patients and eight of these required dose reduction. Mild increases in total bilirubin were noted in two patients and mild hyperuricemia in eight. Sixteen children had grade 3 and four children had grade 4 neutropenia. None of the cases of severe neutropenia were associated with serious infections. There was no grade 3 or 4 thrombocytopenia. No discontinuations because of thrombocytopenia occurred. Six patients have developed TSH abnormalities on study, one patient had developed mild hypothyroidism and one patient was receiving thyroxin treatment for thyroiditis.

#### **DISCUSSION AND CONCLUSIONS**

As far as can be judged from the limited data available INTRON A 3MIU/m<sup>2</sup> TIW plus REBETOL 15 mg/kg/day has antiviral activity similar to that seen in adults.

The safety profile of the therapy is even more difficult to assess. The types of adverse events appear to be similar to those seen in adults. The relative incidence cannot be judged. However certain adverse events may be less well tolerated and pose greater risks to children. Examples are interferon-induced severe depression, weight loss, nausea and vomiting, and endocrine abnormalities. The teratogenic and mutagenic potential of ribavirin are also of concern. The potential exists for bone marrow toxicity, in particular severe neutropenia to induce life-threatening adverse events (e.g. serious infections). Other adverse events (e.g. hemolytic anemia) might pose lower risk in children in the absence of concomitant diseases.

The sponsor believes that given these risks, patients without evidence of significant liver fibrosis or of rapid disease progression should not be treated. Such patients require careful long-term follow up.

## APPENDIX 4

### **SELECTED CLINICAL NARRATIVES OF SERIOUS ADVERSE EVENTS**

Brief summaries of serious adverse events are provided to illustrate some of the syndromes associated with the study treatments. The cases were selected based on their clinical significance, the adequacy of documentation and the treatment group (preference was given to the Peg 1.5/R arm).

#### **NEUROPSYCHIATRIC DISORDERS**

##### Suicide completed/attempted

Patient 0881, 41-year-old man, Peg 1.5/R arm, with history of mild depression treated with fluoxetine. The patient developed anemia after 4 weeks of treatment (Hgb 8.4 g/dL) and after 8 weeks he experienced joint pain, insomnia, and worsening depression. The dose of fluoxetine was increased. Two weeks later the patient committed suicide by hanging. The investigator considered the suicide possibly related to study medication.

Patient 0944, 48-year-old man, Peg 1.5/R arm, with history of depression and anxiety, no previous suicide attempts. After 2-3 weeks' treatment, the patient experienced irritability and mild depression, and temazepam and fluoxetine were started. At about ten weeks the patient attempted suicide by shooting himself in the right chest. Study treatment was discontinued. The patients recovered from the trauma. The investigator considered the suicidal attempt possibly related to study medication.

##### Aggressive reaction/homicidal ideation, depression/suicidal ideation

Patient 0882, 50-year-old man, on Peg 1.5/R arm, with history of blunt trauma/fractures/coma, and alcohol abuse; no history of depression. The patient experienced fever, arthralgia, myalgia, and depression; fluoxetine was begun. At eight weeks of study treatment he reported thoughts of killing three previous co-workers and himself. Study treatment was terminated. The investigator considered the suicidal ideation possibly related to the study medications.

##### Psychosis, hallucination

Patient 0524, 38-year-old woman, Peg 1.5/R arm, with history of suicide attempt. The patient developed high TSH levels followed by low levels of TSH, agitation and insomnia. Four weeks after the end of study treatment the patient was hospitalized briefly with diagnosis of depression and psychosis (the latter treated with haloperidol). The investigator considered the events possibly related to study treatment.

Patient 0821, 46-year-old man, Peg 1.5/R arm, no previous history of depression, developed mild-moderate depression, severe fatigue, auditory hallucinations, nausea and vertigo. The investigator considered the events probably related to study treatment. The events resolved after reduction of dose of study medication and start of antidepressant drug.

Patient 1467, 47-year-old woman, with symptoms of paranoid schizophrenia since 1987, on no treatment. After eight weeks of study treatment the patient developed delusional thinking, persecutory mania, and hallucinations. Study treatment was discontinued and haloperidol was begun. The paranoid psychosis was judged to be possibly related to study treatment.

Patient 0272, 42-year-old woman, Peg 1.5/R arm. Three weeks after the end of study treatment, global confusion, memory loss, and visual hallucinations developed. Neurologic work-up was unrevealing. The patient was discharged on fluoxetine and was to receive psychiatric follow up. The events were judged to be probably related to study medication.

#### Manic reaction

Patient 0165, 40-year-old woman, Peg 0.5/R arm, history of stable depression and panic disorders treated with sertraline. About 14 weeks after the start of study treatment the patient became very talkative and her partner became concerned about her mood. The patient was admitted to a psychiatric hospital with a diagnosis of manic reaction possibly related to study medication. Study treatment was discontinued.

#### Relapse of drug addiction

Patient 0216, 32-year-old man, PEG 0.5/R arm, history of ethanol and intravenous drug abuse. One month after the start of study drug, the patient developed irritability and nausea and a sedative and antidepressants were begun. The patient began to self-treat with hydrocodone, acetaminophen and propoxyphene, and diazepam. Toxicology screen confirmed the exposure to opiates, benzodiazepines. Study treatment was discontinued. The investigator considered the drug abuse possibly related to study medication.

#### *Reviewer's comments*

*Depression, aggressive reactions, and suicidal and homicidal ideation may be observed in patients with or without previous psychiatric history. Various other serious neuropsychiatric disorders (including psychoses) were associated with study treatment; discontinuation of study treatment was commonly associated with improvement or resolution of the syndrome.*

#### ACCIDENTAL INJURY

Patient 0700, 48-year-old man, I/R arm. After three weeks of study treatment the patient developed mild depression and irritability, fluoxetine was begun. About four weeks later the patient was killed in a single vehicle accident while riding a motorcycle. The investigator considered the accident possibly related to study medication but considered the death unrelated to study medication

Patient 0451, 35-year-old-man, Peg1.5/R arm, experienced fatigue, impaired concentration, and insomnia during study treatment. Three weeks after the end of study treatment the patient was involved in a head-on motor vehicle collision. The patient sustained rib and sternal fractures and had to be extracted from his vehicle, a passenger in the other colliding vehicle died. The investigator considered the event unlikely related to study medication.

Patient 0620, 33-year-old man, PEG1.5/R arm. About nine weeks after start of study treatment the patient was in a motor vehicle accident and sustained multiple fractures, pulmonary contusion, was comatose and required intubation and ventilation. The patient recovered, study treatment was discontinued. The accident was judged to be unrelated to study treatment.

#### *Reviewer's comment*

*Disturbances such as fatigue, impaired concentration and depression may contribute to some of the serious accidental injuries experienced by study patients. At this time there is no evidence in the agency's spontaneous reporting database to support this speculation.*

#### INFECTIONS

##### Cellulitis, sepsis

Patient 0686, 47-year-old-man, Peg 1.5/R arm, with venous insufficiency of lower extremities. The patient developed anemia (Hgb 10.4 from 14.6 g at baseline) further decrease in platelet count (78,000 from 101,000/mm<sup>3</sup> at baseline) and severe neutropenia (0.65 from 1.99/mm<sup>3</sup> at baseline). The patient developed erythema and swelling of left ankle, followed by extension of swelling and erythema to the thigh, T of 105 °F, WBC 10,000/mm<sup>3</sup>, positive blood culture for  $\beta$ strep and negative Doppler ultrasound of the lower extremities. Study treatment was interrupted and antimicrobials administered for cellulitis and sepsis. The cellulitis resolved and treatment was resumed. By the end of the follow-up period the neutropenia had resolved, hemoglobin was 12.6 g/dl, while platelet counts (84,000/mm<sup>3</sup>) remained low. The investigator judged the cellulites and sepsis to be unrelated to study medication.

#### Post-operative infection

Patient 152, 43-year-old man, Peg 1.5/R arm, developed neutropenia (PMNs 1.24/mm<sup>3</sup> from 2.79 at baseline). The patient was hospitalized for right lower quadrant discomfort and an appendectomy was performed. A post-operative wound infection prolonged the hospitalization and was treated with antibiotics. Study medication was resumed. The investigator considered the appendicitis and post-operative complication unrelated to study medication.

#### Injection site abscess

Patient 1775, 39-year-old woman, Peg 1.5/R arm. The patient developed cellulitis and abscess at the peginterferon injection site. Incision and drainage was performed and wound culture grew multiple gram positive and negative bacilli. Antimicrobial treatment was begun and the patient was discontinued from treatment; hematology lab data are not available.

#### Pneumonia

Patient 0865, 47-year-old man, Peg 1.5/R arm. The patient developed anemia, thrombocytopenia and neutropenia. At 22 weeks after the start of treatment the patient was hospitalized with a 3-day history of progressive shortness of breath, cough, fever, chills and pleuritic chest pain. A chest X-ray revealed left upper lobe infiltrates and the patient was diagnosed with community-acquired pneumonia. The patient recovered with antimicrobial treatment and study treatment was continued. Hematology was normal at the end of the follow-up period. The investigator considered the event probably related to study medication.

#### *Reviewer's comment*

*Serious infections were associated with interferon-induced neutropenia in this study. All patients recovered from the infections. The package insert warns about the risk that interferon may induce or aggravate infectious disease. A number of patients underwent appendectomies for abdominal pain and confirmation of the diagnosis was not available in most cases. It cannot be determined if/how interferon-induced symptoms and signs influenced the diagnosis and management of these patients.*

### RESPIRATORY SYSTEM

#### Bronchiolitis obliterans

Patient 1236, 63-year-old woman, Peg 1.5/R arm, no history of tobacco abuse and no personal or family history of asthma. Developed asthenia, dyspnea with wheezing and at week 13 of study treatment drug-related bronchiolitis obliterans was diagnosed based on a chest X-ray and pulmonary function tests. Study treatment was discontinued and inhaled corticosteroids were begun. A course of oral corticosteroids was planned. The investigator considered the pneumonitis probably related to study medication.

### CARDIOVASCULAR SYSTEM

#### Chest pain, angina

Patient 1631, 68-year-old woman, I/R arm, no history of cardiac disease. Hemoglobin decreased to 11.9 g/dl from 14.3 g/dl at baseline. Chest pain developed and a stress test was positive. Patient was subsequently hospitalized for angina and a myocardial infarct was excluded. Study treatment was discontinued and  $\beta$ blocker and nitroglycerin were begun. The investigator considered the angina pectoris to be possibly related to study medications.

#### Cardiomyopathy

Patient 0062, 40-year-old man, Peg 1.5/R arm, normal baseline ECG. Between 4-8 months after the start of treatment the patient developed sharp, crampy sensation in the left chest which radiated to the left arm, fatigue, and abdominal cramps. An ECG showed tachycardia and left bundle branch block. Dyspnea and orthopnea developed. Study treatment was terminated. A dobutamine echocardiogram revealed cardiomyopathy. Cardiac catheterization revealed an ejection fraction of 20% with global hypokinesis and normal coronary arteries. The investigator considered the cardiomyopathy possibly related to study medications.

#### Edema, pleural and/or pericardial effusion

Patient 1231, 56-year-old woman, Peg 1.5/R arm, history of hypertension treated since 1996. At week 32 edema of lower limbs was noted and within few weeks pleural and pericardial effusion developed. No cardiac failure and no renal failure were noted. Pericarditis was suspected. Study medications were discontinued and diuretics administered with some regression of the effusions. The investigator considered the event possibly related to study medication.

Patient 0659, 59-year-old woman, in I/R arm, 2 months after start of study treatment developed dyspnea, a drop in hemoglobin (11.1 g/dL from 14.8 g/dL at baseline), lower extremity edema, and 30-pound weight gain. An echocardiogram was normal; diuretics were begun. Superficial thrombophlebitis of left calf was diagnosed; an antimicrobial was administered. Generalized edema and dyspnea worsened and pleural and pericardial effusions were identified. Study treatment was discontinued. An echocardiogram showed collapse of the right ventricle during systole, pericardiocentesis was performed with removal of 500 ml of bloody fluid. The edema was not resolved at the end of follow-up. No final diagnosis given. The investigator considered the events possibly related to study medication.

#### GASTROINTESTINAL SYSTEM

##### Ischemic colitis

Patient 0445, 60 year-old woman, Peg 1.5/R arm. Study medications were reduced for anemia (Hgb 11 g/dl compared to 13.5 g/dl at baseline) and then discontinued for fatigue. Four months after the end of treatment rectal bleeding developed and colonoscopy showed evidence of ischemic colitis

##### Pancreatitis

Patient 0991, 64-year-old man, Peg 1.5/R arm. The patient developed anemia and six weeks after the start of study treatment the patient was hospitalized with acute pancreatitis. The amylase was 2000(normal range 36-128 U/L) and lipase was 1400 (6-32 U/L). Treatment with insulin was required for hyperglycemia. Latest examination available revealed continuation of symptoms and incomplete resolution of pancreatitis. Study medication was discontinued. The investigator initially considered the pancreatitis unrelated to study medication.

Patient 0435, 40 year-old man, I/R arm, history of intermittent epigastric pain, nausea, vomiting treated with proton pump inhibitor. During the treatment period the patient was hospitalized thrice for vomiting and dehydration, GERD, and for constipation. A diagnosis of pancreatitis was made and he was hospitalized twice more with diagnosis of chronic pancreatitis, during one hospitalization pericarditis was diagnosed. Study treatment was discontinued. In the follow up period the patient was hospitalized with bouts of chronic pancreatitis twice. The investigator considered the pancreatitis unrelated to study medications.

##### *Reviewers comment*

*Pancreatitis is known to be associated with interferon  $\alpha$  and ribavirin. No other etiology was identified in these illustrative cases. The package insert recommends that peginterferon/ribavirin be discontinued in patients with diagnosis of pancreatitis.*

##### Liver biopsy complications

The following complications were observed in study patients: pneumothorax (n=1), gallbladder injury (n=2), hemoperitoneum, laparotomy to control bleeding (n=1).

##### *Reviewer's comment*

*The usefulness of data from the post-treatment liver biopsy is limited, and the risks of the procedure are significant.*

#### AUTOIMMUNE DISEASE

##### Sarcoidosis, non-caseating granulomas

Patient 0363, 49 year-old woman, Peg1.5/R arm, with baseline chest-x ray showing hyperinflation,

apical pleural thickening, and scar in right apex. Patient developed hypothyroidism, treated with thyroxin, and anemia (Hgb 9.7 g/dl). Patient progressively developed cough, dyspnea, tachycardia (HR120) and bibasilar crackles with CXR consistent with interstitial lung disease. CT showed mediastinal adenopathy and lung biopsy showed granulomas. Study treatment was terminated after 6 months. Diagnosis: sarcoidosis possibly related to study treatment.

Patient 1265, 50 year-old woman, I/R arm, with history of pulmonary sarcoidosis in 1978. During study treatment the patient developed anemia (Hgb 9.9 g/dl). Near the end of the treatment period biopsy of skin papules showed granulomas. Chest-x ray post-treatment showed bilateral interstitial/alveolar infiltrates. Diagnosis: reactivation of sarcoidosis probably related to study treatment.

Patient 1676, 42-year-old woman, Peg1.5/R arm, developed adenopathy and granulomatous skin lesions. Diagnosis: probable sarcoidosis related to study treatment.

Patient 653, 49 year-old man, Peg 1.5/R arm, a post-treatment liver biopsy showed non-caseating granulomas of liver, a work up was begun. Upon further review of pretreatment biopsy few small granulomas were seen in periportal areas. The provisional diagnosis was granulomatous lesion aggravated, possibly related to study medication.

#### *Reviewer's comment*

*The association of sarcoidosis is consistent with induction or exacerbation of other immune diseases by interferon alphas. The association will be cited in the package insert.*

#### ENDOCRINE DISORDERS

##### Thyroiditis, hyperthyroidism, hypothyroidism

Patient 1692, 45-year-old man, Peg 0.5/R arm. Study treatment was interrupted after six months because of irritability, and was terminated at 10 months because of asthenia. Five weeks post-treatment sinus tachycardia, weight loss, muscle weakness, undetectable TSH and a heterogeneous goiter were documented and treatment with anti-thyroid drugs and beta-blockers was begun. The hyperthyroidism was considered related to study medication.

Patient No: 1689, 36-year-old man, with normal TSH at baseline. After six months of study treatment hypothyroidism was noted with TSH =24.73 MU/L (normal 0.49-4.67), T4 =8 picomol/L (normal 10-20), T3 =5.2 picomol/L (normal 3.5 -8) and anti-thyroid peroxidase antibodies = 416 U/ml (normal <60). The patient complained of dry skin. Study treatment was continued and levothyroxin was begun. Hypothyroidism was considered probably related to study medication.

##### Diabetes

Patient 0705, 44-year-old woman, I/R arm, obese with family history of diabetes, developed hyperglycemia during study treatment. The patient was hospitalized with uncontrolled diabetes, blurred vision nausea and vomiting. Study treatment was discontinued and insulin treatment begun. The investigator considered the diabetes to be possibly related to study treatment.

#### OPHTHALMOLOGIC EVENTS

##### Visual Loss, retinal artery or vein thrombosis

Patient 1286, 63-year-old man, Peg 1.5/R arm, no diabetes, no arterial hypertension, no glaucoma, and no vascular disorder. Patient developed decreased visual acuity in his right eye. Obliteration of the retinal central vein was diagnosed; visual acuity was 6/10; ophthalmologic evaluation otherwise negative. Patient underwent normovolemic hemodilution and study treatment was discontinued.

Patient 1222, 53 year-old man, with history of hypertension and protein S deficiency. At ten months of study treatment he reported mild decreased vision in the right eye. At 11months he developed sudden, complete loss of vision in the right eye. A diagnosis of retinal vein thrombosis was made. The event was judged to be possibly related to study treatment.

Patient 1690, 61-year-old woman with history of diabetes not currently treated. After six months of study treatment decreased visual acuity was noted. At nine months transient loss of vision in the right eye occurred. Examination revealed cotton wool spots in the left eye and a retinal hemorrhage in the right eye. Study treatment was discontinued.

Patient 0963, 37-year-old man, I/R arm, no history of vascular disease. Eight weeks after start of study medication, the patient experienced a sudden pain in his head, became lightheaded and had blurred vision bilaterally. He lost vision in his left eye. Retinal artery thrombosis was diagnosed, the ocular pressure was dropped and the clot propagated through the superior and inferior retinal branches and vision improved, anticoagulants were begun. Visual acuity was 20/90 in the left eye and normal in the right eye. The investigator considered the retinal thrombosis unlikely related to study medications; the sponsor considers it possibly related.

Patient 0061, 44-year-old man, Peg 1.5/R arm. At 13 weeks after start of study treatment visual loss in the right eye was reported and diagnosis of right optical papillitis was made. Study medications were discontinued; the investigator considered the event probably related to study medication.

*Reviewer's comment*

*Loss of vision will be mentioned in the package insert. The need for ophthalmologic examination at baseline and need for prompt evaluation of visual symptoms will be mentioned.*

#### HEMATOLOGIC EVENTS

##### Thrombocytopenia

Patient 0487, 43 year-old man, I/R arm, history of occupational arsenic exposure and hypothyroidism. Platelet count 140,000 at end of treatment. Thrombocytopenia began 4 weeks later (nadir 18,000), Bone marrow showed megakaryocytic hyperplasia. Platelets returned to normal with high dose corticosteroids. Diagnosis: ITP possibly related to study treatment.

#### METABOLIC DISORDERS

##### Gout

Patient 1282, 60-year-old man, Peg 1.5/R arm, developed prostatitis requiring hospitalization and antimicrobial treatment. The patient was treated with colchicine for diagnosis of gout attack and allopurinol was begun.

#### DERMATOLOGIC EVENTS

##### Urticaria

Patient 1254, 55-year-old woman, Peg 1.5/R arm who at week 8 of study treatment developed pruritus at the injection site extending to thighs and trunk. Three weeks later urticaria developed at the same sites and became generalized. Study treatment was discontinued and corticosteroids were begun. The investigator considered the event probably related to study medication.

##### Phototoxic reaction

Patient 1241, 62-year-old man, Peg 1.5/R arm, five weeks after the end of treatment, the patient experienced after sun exposure a severe erythematous reaction of limbs, face and shoulder accompanied with fever and pain at skin pressure. The patient (a dermatologist/allergologist), diagnosed a phototoxic reaction, and corticosteroids were administered. The investigator considered the photosensitivity reaction to be related to study medication.

### **SELECTED NARRATIVES OF SERIOUS ADVERSE EVENTS FROM SAFETY UPDATES**

##### Psychiatric adverse events: mania/bipolar disorder

Patient 2000-11-0169. This 39 year-old woman had no previous psychiatric history and received peginterferon and lamivudine for 4 months for chronic hepatitis B. The patient was hospitalized for

depression and a diagnosis of bipolar affective disorder was made. The event was considered possibly related to peginterferon and the antiviral treatment was discontinued.

Patient 2000-12-0367. This 23 year-old man with history of drug abuse, mild depression and anxiety received peginterferon and ribavirin for 11 weeks for treatment of chronic hepatitis C. The patient was hospitalized after a suicide attempt and development of homicidal ideation. The diagnosis of bipolar disorder and schizophrenia was made, antiviral treatment was discontinued, and lithium was begun. The investigator considered the events possibly related to peginterferon.

Patient 2001-04-0069. This 39 year-old man with history of drug addiction and HIV encephalopathy, received peginterferon/ribavirin for chronic hepatitis C. Four weeks after the start of treatment the patient was hospitalized for a manic reaction considered possibly related to study drugs.

*Reviewer's comment.*

*Manic episodes were also observed in the phase 3 study. The label for peginterferon and the proposed label for peginterferon/ribavirin do not cite bipolar disorder or manic reaction.*

*Plan: Add these two disorders to the WARNINGS: Neuropsychiatric events- section of both labels.*

Pulmonary adverse events

Patient 2001-02-1249. This 69-year-old man on IFN/R developed neutropenia and respiratory failure due to bilateral interstitial pneumonia after the first dose of PEG/R. After the patient improved, a second dose of peginterferon was given with recurrence of interstitial pneumonia, respiratory failure and granulocytopenia. The patient died due to respiratory and renal failure. No infectious etiology for the pneumonitis was identified. The death was considered possibly related to peginterferon.

*Reviewer's comments*

*The label for peginterferon describes the association of pneumonitis with peginterferon and interferon. The label recommends close monitoring of patients with pulmonary infiltrates or pulmonary function impairment. Lethal pneumonitis has been observed with two peginterferon products. One patient with one episode of peginterferon-induced pneumonitis died with respiratory failure upon rechallenge.*

*Plan: Revise the WARNING: Pulmonary disorder-section of the label to: indicate that peginterferon induces pneumonitis with respiratory failure, cite one case of positive rechallenge warn against restarting peginterferon in patients with serious pulmonary reactions.*

Injection site necrosis

Patient 2001-01-1472. This 73 year old woman with Parkinson's disease, HCV associated with vasculitis, polyneuropathy and cryoglobulinemia was treated with peginterferon 100 µg SC weekly and ribavirin 800 mg PO for 2 weeks. Leukopenia developed and was associated with development of skin necrosis at the IFN injection sites. The investigator considered the necrosis to be probably related to IFN.

Patient 1999-03-0682. This 39-year-old man with melanoma developed a firm erythematous 2x2 cm lesion at a site of injection of peginterferon 6 µg/kg/wk SC. The dose was reduced to 4.5 µg/kg/wk. The patient developed a 6x4 cm area of necrosis at the site of his last injection. The necrotic area was said to measure 0.5 inch in thickness. And was treated with a topical corticosteroid and antimicrobial. The sponsor considered the event to be possibly related to peginterferon.

*Reviewer's comment*

*Plan: Add this information to the Adverse Reaction section of the package insert.*

Bone marrow toxicity

Patient 2000-01-0803. This 49 year-old woman received peginterferon for chronic myelogenous leukemia. Peginterferon was held, restarted at a reduce dose and ultimately discontinued after the

patient's WBC decreased from 13.6 to 1.5. The patient's neoplastic disease underwent blast transformation and then developed into acute myelogenous leukemia. Antineoplastic drugs were started. The patient developed pancytopenia and succumbed to enterococcal sepsis. The investigator judged the events to be possibly related to peginterferon.

Patient 2001-02-1249. This 64 year-old man with chronic HCV underwent liver-kidney transplantation and was treated with Interferon 3 MU TIW plus ribavirin 400 mg PO qd to prevent infection of the liver allograft. Interferon was substituted by peginterferon 0.5µg/kg/week. Aplasia was diagnosed and peginterferon was discontinued. The patient improved and peginterferon was restarted. Aplasia recurred. The investigator considered the event to be possibly related to peginterferon and ribavirin.

*Reviewer's comment*

*The evidence supporting the link between peginterferon and aplastic anemia is not strong and the cases are not well documented. The association of interferon and aplastic anemia is already cited in the label.*

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**BLA:** STN-103949  
*PEG-Intron+REBETOL for the treatment of chronic hepatitis C.*  
*Schering Corporation*

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**Date:** August 3, 2001

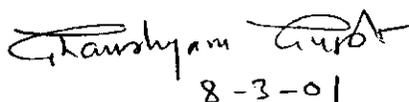
**Reviewer:**

J. Tiwari, Ph.D.

  
8-3-01

**Through:**

Ghanshyam Gupta, Ph.D.  
Chief, Therapeutics Evaluation Branch

  
8-3-01

**To:**

Libero Marzella, M.D.

**cc:**

HFM-99/DCC: BLA STN-103949  
HFM-588/Ms. Tyson-Medlock  
HFM-210/Dr. Ellenberg  
HFM-210/Dr. Lachenbruch  
HFM-210/Chron - File: OP-5.7

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The clinical and statistical issues related to the review of this BLA have been discussed with the clinical staff from the Division of Clinical Trial Design and Analysis (Drs. Louis Marzella, William Schwieterman, and Karen Weiss). This reviewer has analyzed the electronic data submitted by the sponsor. Results of our analyses are consistent with those given in the clinical report submitted by the sponsor. This review will summarize the observed results on the primary and key secondary efficacy endpoints.

## Study Design

This submission consists of a single randomized, open-labeled trial in which the following two PEG-Intron/REBETOL regimens were compared to the standard therapy of INTRON A/REBETOL (current standard of care) for treatment of chronic hepatitis C in previously untreated adult subjects:

- |                                     |  |
|-------------------------------------|--|
| <b>Treatment Arm A (PEG 1.5/R):</b> | PEG-Intron (1.5 mcg/kg QW/ribavirin (1000/1200 mg/day) for 4 weeks then PEG-Intron (0.5 mcg/kg QW/ribavirin (1000/1200 mg/day) for 44 weeks. |
| <b>Treatment Arm B (PEG 0.5/R):</b> | PEG-Intron (1.5 mcg/kg Qw)/ribavirin (800 mg/day) for 48 weeks.  |
| <b>Treatment Arm C (I/R):</b>       | INTRON A (3 MIU TIW/ribavirin (1000/1200 mg/day) for 48 weeks (standard of care).  |

All patients were followed for additional 24 weeks.

Eligible subjects were randomized equally to one of the three study arms. Randomization was stratified on the basis of HCV genotype (genotype 1 vs. non-1) and the presence or absence of cirrhosis (assessed by a local pathologist).

The primary efficacy variable was loss of detectable serum HCV-RNA/qPCR (<100 copies/ml) at the end of 24 weeks of follow-up. Serum HCV-RNA/qPCR testing was done by a central laboratory  $\text{C}$   $\uparrow$ . Only subjects with positive HCV-RNA assay at the baseline were eligible to enroll in the study.

Response was assessed as follows:

- Responder:** *A subject was classified as a responder at a given time point, if detectable serum HCV-RNA/qPCR was negative (<100 copies/ml) at that time point.*
- Sustained Responder:** *A subject was classified as a sustained responder if the subject was a responder (HCV-RNA negative) at 24 weeks of follow-up. All other subjects, including those who discontinued before the required serum HCV-RNA/qPCR evaluations were obtained were considered nonresponders.*
- Relapser:** *A subject was classified as a relapser if the subject was a responder at the end of treatment and became HCV-RNA positive at follow-up Week 24.*

The protocol specified primary treatment comparison was PEG 1.5/R versus I/R. The non-inferiority of the PEG 1.5/R was to be evaluated by using a delta value of 10% of the control response rate (i.e., the response rate in I/R group).

The protocol also included the following secondary efficacy endpoints:

1. Normalization of ALT at the end of treatment and at the end of follow-up.
2. Loss of HCV-RNA at the end of treatment.
3. Improvement and change from baseline in biopsy scores (Knodell, I+II+III, IV and Metavir scores).

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## Results and Reviewer's Comments

### 1. Primary Efficacy Analysis: PEG 1.5/R versus I/R

The observed end of treatment and the end of follow-up response rates are given in Table 1. Based on the protocol specified criterion (i.e.,  $\Delta=10\%$  of the end of follow-up response rate in I/R group), the non-inferiority margin is  $-4.57\%$ . The difference between PEG 1.5/R and I/R at the end of follow-up is  $+5.9\%$  with a 95% confidence interval from  $0.18\%$  to  $11.63\%$ . Thus, PEG 1.5/R meets the criterion of non-inferiority. In fact, as the 95% confidence interval for the observed difference indicates, the sustained response rate in PEG 1.5/R group is significantly higher than that in the I/R group with a  $P=0.037$  (Table 1).

In patients with HCV genotype 1, the response rates in PEG 1.5/R and I/R groups are  $40.52\%$  (141/348) and  $32.65\%$  (112/343), respectively. This difference is also significant with a P-value of  $0.026$ . For patients with non-genotype 1 the observed response rates were  $75.46\%$  (123/163) in PEG 1.5/R group and  $73.46\%$  (119/162) in the I/R and this difference is not significant ( $P=0.9$ ).

### 2. Primary Efficacy Analysis: PEG 0.5/R versus I/R

Although PEG 0.5/R versus I/R was not the protocol specified primary comparison of this study, it is one of two PEG doses evaluated in this study and, thus, it is a very important component of the primary analysis and evaluation of the safety and efficacy of PEG-Intron. The difference between PEG 0.5/R and I/R at the end of follow-up is  $+0.8\%$  with a 95% confidence interval from  $-4.72\%$  to  $+6.53\%$ . Thus, Peg 0.5/R *does not* meet the criterion of non-inferiority. The P-value for this comparison is  $0.778$ .

The response rates in the subgroup of HCV genotype 1 patients were  $75.15\%$  (115/349) in PEG 0.5/R and  $73.46\%$  (112/343) in I/R patients. The difference between the two treatment arms was not significant ( $P=0.8$ ). No significant difference ( $P=0.8$ ) was seen between the two arms in the patients with non-genotype 1 virus ( $124/165=75.15\%$  in PEG 0.5/R versus  $119/162=73.46\%$  in I/R).

### 4. Secondary Efficacy Endpoint: ALT Response

The ALT response at the end of follow-up was significantly increased in the PEG 1.5/R group but not in the PEG 0.5/R group (Table 1). As the data in Table 3 indicate, only a very small fraction of sustained virologic responders did not normalize their ALT ( $3\%$  in PEG 1.5/R,  $8\%$  in PEG 0.5/R, and  $3\%$  in I/R). It should be noted that the ALT response used to be the primary endpoint in early interferon and hepatitis C studies.

**5. Secondary Efficacy Endpoint: Improvement in Hepatic Inflammation Knodell (I+II+III) and Hepatic Fibrosis (Knodell (IV) Measured by Mean Change from Baseline**

Liver biopsy data were in 339 of the 511 patients (66.3%) in PEG 1.5/R, 361 of 514 (70.2%) in PEG 0.5/R, and 334 of 505 (66.1%) in I/R.

The mean changes from baseline in hepatic inflammation (Knodell HAI (I+II+III) in all subjects and three subgroups - sustained responders, relapsers and nonresponders – are given in Table 4. The results for the hepatic fibrosis (Knodell (IV) are given in Table 5. All three groups showed very similar improvement in hepatic inflammation and hepatic fibrosis.

**6. Secondary Efficacy Endpoint: Improvement in Hepatic Inflammation Knodell (I+II+III) and Hepatic Fibrosis (Knodell IV) Measured by Proportion of Patients Showing Decrease in Score**

The “improvement” in this protocol was defined as proportion of patients showing a minimum improvement (decrease) of at least 2 units in their Knodell score. These results for Knodell (I+II+III) and hepatic fibrosis (Knodell IV) are given are in Tables 6 and 7. Here again, the results in all three groups are very similar.

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Table 1. Virologic response.

Patient Group	Treatment Arm A PEG 1.5/R N=511	Treatment Arm B PEG 0.5/R N=514	Treatment Arm C I/R N=505	Treatment Comparison A vs. C	Treatment Comparison B vs. C
<b>End of Treatment</b>					
All Subjects	65% (333/511)	56% (289/514)	54% (271/505)	P<0.001*	P=0.371*
HCV Genotype 1	54% (188/348)	43% (149/349)	42% (143/343)		
HCV Genotype 2/3	93% (136/147)	88% (134/153)	84% (122/146)		
HCV Genotype 4/5/6	56% (9/16)	50% (6/12)	38% (6/16)		
<b>End of Follow-Up</b>					
All Subjects	52% (264/511)	46% (239/514)	46% (231/505)	P=0.037*	P=0.778*
HCV Genotype 1	41% (141/348)	33% (115/349)	33% (112/343)	P=0.026*	P=0.884*
HCV Genotype 2/3	78% (115/147)	78% (120/153)	77% (113/146)		
HCV Genotype 4/5/6	50% (8/16)	33% (4/12)	38% (6/16)		

\* Logistic regression Analysis using HCV genotype and presence of cirrhosis at baseline

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Table 2. Normalization of ALT: At the end of treatment and at the end of follow-up.

	Treatment Arm A PEG 1.5/R N=511	Treatment Arm B PEG 0.5/R N=514	Treatment Arm C I/R N=505
End of treatment	65.0% (332)	63.4% (326)	69.3% (350)
End of follow-up	53.6% (274) <sup>*</sup>	8.1% (247) <sup>**</sup>	46.7% (236)

\* A versus C P=0.028

\*\* B versus C P=0.673

Table 3. ALT Response in all Virologic Responders.

	Treatment Arm A PEG 1.5/R N=511	Treatment Arm B PEG 0.5/R N=514	Treatment Arm C I/R N=505
End of follow-up <sup>1</sup>	97.0% (256/264)	92.5% (221/239)	96.5% (223/231)

<sup>1</sup> Sustained responders with normal ALT/all sustained responders.

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Table 4. Mean change in hepatic inflammation by Virologic Response - Knodell HAI (I+II+III)

	Treatment Arm PEG 1.5/R	Treatment Arm PEG 0.5/R	Treatment Arm I/R
All Subjects <sup>1</sup>	-3.4 (N=339)	-3.4 (N=361)	-3.4 (N=334)
Sustained Responders	-5.2 (N=198)	-5.3 (N=191)	-5.3 (N=181)
Relapsers	-0.7 (N=42)	-1.8 (N=30)	-2.2 (N=23)
Nonresponders	-0.8 (N=99)	-1.2 (N=140)	-0.9 (N=130)

<sup>1</sup> All subjects with paired biopsies.

Table 5. Mean change in hepatic Fibrosis by Virologic Response - Knodell (IV)

	Treatment Arm PEG 1.5/R	Treatment Arm PEG 0.5/R	Treatment Arm I/R
All Subjects <sup>1</sup>	-0.1 (N=339)	-0.2 (N=361)	-0.2 (N=334)
Sustained Responders	-0.3 (N=198)	-0.3 (N=191)	-0.2 (N=181)
Relapsers	0.3 (N=42)	-0.2 (N=30)	-0.2 (N=23)
Nonresponders	0.2 (N=99)	-0.1 (N=140)	-0.1 (N=130)

<sup>1</sup> All subjects with paired biopsies.

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Table 6. Hepatic inflammation by Sustained Virologic Response – Knodell HAI (I+II+III)

	Histology	Treatment Arm PEG 1.5/R	Treatment Arm PEG 0.5/R	Treatment Arm I/R
All Subjects <sup>1</sup>		N=339	N=361	N=334
	Improved	68% (232)	70% (254)	69% (232)
	No Change	22% (74)	22% (80)	21% (71)
	Worse	10% (33)	7% (27)	9% (31)
Sustained Responders		N=198	N=191	N=181
	Improved	90% (178)	90% (171)	91% (164)
	No Change	8% (16)	10% (19)	9% (16)
	Worse	2% (4)	1% (1)	1% (1)
Relapsers		N=42	N=30	N=23
	Improved	38% (16)	60% (18)	61% (14)
	No Change	40% (17)	20% (6)	39% (9)
	Worse	21% (9)	20% (6)	0%
Nonresponders		N=99	N=140	N=130
	Improved	38% (38)	46% (65)	42% (54)
	No Change	41% (41)	39% (55)	35% (46)
	Worse	20% (20)	14% (20)	23% (30)

<sup>1</sup> All subjects with paired biopsies.

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Table 7. Hepatic fibrosis by Sustained Virologic Response – Knodell (IV)

	Histology	Treatment Arm PEG 1.5/R	Treatment Arm PEG 0.5/R	Treatment Arm I/R
All Subjects <sup>1</sup>		N=339	N=361	N=334
	Improved	21% (71)	19% (69)	20% (66)
	No Change	65% (220)	72% (261)	71% (237)
	Worse	14% (48)	9% (31)	9% (31)
Sustained Responders		N=198	N=191	N=181
	Improved	26% (51)	21% (40)	20% (37)
	No Change	67% (132)	73% (140)	73% (133)
	Worse	8% (15)	6% (11)	6% (11)
Relapsers		N=42	N=30	N=23
	Improved	12% (5)	23% (7)	26% (6)
	No Change	62% (26)	63% (19)	61% (14)
	Worse	26% (11)	13% (4)	13% (3)
Nonresponders		N=99	N=140	N=130
	Improved	15% (15)	16% (22)	18% (23)
	No Change	63% (62)	73% (102)	69% (90)
	Worse	22% (22)	11% (16)	13% (17)

<sup>1</sup> All subjects with paired biopsies.

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