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INTRODUCTION

The purpose of this meeting is: 1) to update the Antivirals Advisory Committee on the data supporting the safety and efficacy of PEGASYS (Pegylated Interferon alfa 2a) in combination with COPEGUS(ribavirin) for the treatment of adult patients with chronic hepatitis C infection and 2) to discuss questions about dosing that may result in request for postmarketing studies.

Filing of Application

On -----, Hoffman-LaRoche Corporation submitted to FDA a License Application for PEGASYS (peginterferon alfa 2a) and COPEGUS (ribavirin, USP) combination therapy for the treatment of chronic hepatitis C.

Study Products

Peginterferon alfa-2a (PEG-IFN) 180 µg administered sc qw
Ribavirin 200 mg/tablet administered po daily in split doses (final dose 1000 or 1200 mg depending on body weight) and taken with food.

Comparator product: Interferon alfa-2b 3 (IFN) 3 MIU administered sc tiw
Ribavirin 200 mg/capsule (Schering/ICN brand) administered po daily in split doses (final dose 1000 or 1200 mg depending on body weight) and taken with food.

Chronic Hepatitis C

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. Recovery from acute infection occurs in approximately 15% of adults with the remainder developing chronic hepatitis C infection. Patients with chronic HCV infection typically have persistent viremia and in most cases abnormal ALT levels.

In the US, approximately 50% of children and 85% of adults infected with HCV develop chronic hepatitis leading to an overall prevalence of 2.7 million individuals in the US with chronic hepatitis C infection. After decades, liver cirrhosis develops in about 20% of adults with chronic HCV infection within 20 years and 30% within 30years. In children with chronic HCV the incidence of cirrhosis is lower compared to adults possibly due to the shorter duration of infection or a slower progression of disease. The development of cirrhosis is associated with liver failure, with portal hypertension with its related complications and with the development of hepatocellular carcinoma. Chronic HCV infection causes approximately 12,000 deaths per year and is the primary reason for liver transplantation in the US. Genotype 1 is the most prevalent HCV genotype in the US (approximately 70% overall) and is less likely to respond to treatment compared with HCV genotypes 2 and 3. In addition to genotype 1, other factors associated with diminished response to treatment are: high circulating HCV viral load ($>2 \times 10^6$ copies/ml serum) and the presence of cirrhosis on histology.

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 can induce loss of detection of circulating HCV RNA, normalization of serum transaminase levels, and a modest reduction in liver inflammation. At 6 months following completion of alpha interferon monotherapy, the proportion of patients with undetectable HCV RNA is low (<20%). The addition of ribavirin to alpha interferon treatment roughly doubles the proportion of responders to approximately 40%. At the time the safety and efficacy trials for this submission were undertaken, alpha interferon and ribavirin represented the most efficacious therapy available for chronic hepatitis C. Peginterferon alfa 2b, both as monotherapy and in combination with ribavirin, was approved for the treatment of chronic hepatitis C in 2001.

Arguably, the risk/benefit of interferon alfa monotherapy for chronic HCV is no longer acceptable especially for patients with poor prognostic factors such as genotype 1 or high viral titers. Fewer than 10% of patients with chronic hepatitis C with cirrhosis or genotype 1 achieve sustained viral response with interferon alfa monotherapy.

There is no definitive evidence that the loss of detection of circulating HCV RNA six months after the end of treatment (sustained viral response), which is the primary outcome measure of most studies, will decrease the incidence of serious long-term outcomes including progression of liver disease to cirrhosis and the development of hepatocellular carcinoma.

Alpha interferons adversely affect a number of organ systems and may induce a number of serious toxicities including neuropsychiatric disorders, autoimmune disorders, ischemic disorders and disorders of host defenses. The majority of patients on alpha interferons experience fatigue and flu-like symptoms; alpha interferons also commonly induce nausea, vomiting, anorexia and weight loss. They may induce liver decompensation in patients with chronic liver failure. Interferons are abortifacients.

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

CLINICAL STUDIES OF PEGASYS AND COPEGUS

Study Hypothesis: The pegylation of interferon alfa 2a will increase the treatment response and tolerability of that agent against chronic hepatitis C due to the improved pharmacokinetic properties that result from pegylation with increased exposure to more consistent serum concentration for 7 days and the possibility of once a week dosing.

The clinical development program comprised 19 phase 1 clinical pharmacology studies (14 to support PEG-IFN alfa-2a and 5 to support Ribavirin). The 14 clinical pharmacology studies of PEG-IFN alfa-2a were part of the monotherapy development program. Table 1 lists the principal clinical safety and efficacy studies.

Table 1. Clinical Studies of Peginterferon alfa-2a and Ribavirin in CHC

Protocol No. Study Objectives	Treatment Duration	N	Treatment Groups
NV15800 Phase 2 Safety and PK study	48 wks (genotype 1)	16	PEG-IFN alfa-2a 180 ig sc qw ribavirin 1000/1200 mg po qd
	24 wks (genotype non-1)	4	PEG-IFN alfa-2a 180 ig sc qw ribavirin 1000/1200 mg po qd
NV15801 Phase 3 Efficacy and safety	48 wks	227	PEG-IFN alfa-2a 180 ig sc qw placebo po qd
		465	PEG-IFN alfa-2a 180 ig sc qw ribavirin 1000/1200 mg po qd
		457	IFN alfa-2b 3 MIU sc tiw ribavirin 1000/1200 mg po qd
NV15942 Phase 3 Treatment duration (24 vs.48 wks) and ribavirin dose (800 vs. 1000/1200 mg)	24 wks	207	PEG-IFN alfa-2a 180 ig sc qw ribavirin 800 mg po qd
	24 wks	280	PEG-IFN alfa-2a 180 ig sc qw ribavirin 1000/1200 mg po qd
	48 wks	361	PEG-IFN alfa-2a 180 ig sc qw ribavirin 800 mg po qd
	48wks	436	PEG-IFN alfa-2a 180 ig sc qw ribavirin 1000/1200 mg po qd

Including patients participating in the two pivotal studies to be discussed, a total of 1377 patients have received PEG-IFN alfa 2a alone in a range of doses but predominantly 180µg sc as part of the phase 1 clinical pharmacology studies; 357 patients have been exposed to Roche's ribavirin alone and 1843 have been exposed to the combination of PEG-IFN-alfa 2a plus Roche's ribavirin

SUMMARY OF PHASE 2 STUDY

The phase 2 study, NV15800 was a randomized, open label study in patients with chronic hepatitis C without cirrhosis in which all patients received PEG-IFN alfa-2a and ribavirin combination therapy. The major focus of this study was to ascertain the impact of food upon ribavirin absorption as well as the safety of the combination of peginterferon alfa 2a and ribavirin. Given the very few patients studied, the conclusions that can be drawn from this study are very limited. The study will not be considered further here. No dose-ranging studies of PEG-IFN in combination with ribavirin were carried out.

RATIONALE FOR SELECTION OF DOSAGE OF PEGINTERFERON AND RIBAVIRIN FOR PHASE 3

The dose of peginterferon was selected on the basis of analyses of data of peginterferon monotherapy. The efficacy of peginterferon alfa-2a monotherapy in adult patients not previously treated was evaluated in four clinical studies. These trials were comparative, open-label, randomized, with 48-week of therapy followed by 24 weeks of follow-up. A total of 1600 patients were enrolled, 996 patients were treated with PEGASYS.

Table 2. Clinical Studies of Peginterferon alfa-2a Monotherapy in CHC

Study Design	Treatment Regimen (48 week duration)	N	Conclusions
NV15489 Phase 2 randomized, open- label, ascending dose	Peginterferon: 45 µg qw	(20)	90 and 180 µg doses chosen for exploration in phase 3
	90 µg qw	(20)	
	180 µg qw	(45)	
	270 µg qw	(41)	
	Interferon 3 MIU tiw	(33)	
NV15495 Phase 3 randomized, open- label	Interferon 3 MIU tiw	(88)	Peginterferon 180 µg superior to IFN for virologic response
	Peginterferon 90 µg qw	(96)	
	Peginterferon 180 µg qw	(87)	
NV15496 Phase 3 randomized, open- label	Interferon 3 MIU tiw	(214)	Peginterferon 180 µg and 135 µg superior to IFN for virologic response. Responses in the two peginterferon groups similar to each other
	Peginterferon 135 µg qw	(215)	
	Peginterferon 180 µg qw	(210)	
NV15497 Phase 3 randomized, open- label	Interferon 6 MIU tiw x12 wks then 3 MIU tiw x36 wks	(264)	Peginterferon superior to IFN for virologic and biochemical response
	Peginterferon 180 µg qw	(267)	

The number of responders to peginterferon alfa-2a monotherapy was higher than the number of responders to unpegylated interferon alfa-2a monotherapy. The addition of ribavirin to unpegylated interferon alfa increases the number of responders. The sponsor hypothesized that the addition of ribavirin to peginterferon alfa-2a would further increase the number of responders.

The rationale for dose of peginterferon alfa-2a selected for the phase 3 studies was in part based on the analysis of treatment response and safety in peginterferon monotherapy study NV15496. In that study the sustained viral response achieved by both 135µg and 180µg doses of peginterferon once weekly SC were indistinguishable. The sponsor observed that the histologic responses in the peginterferon 135µg group and the interferon alfa-2a group were not different. However the histologic response of the peginterferon 180µg group appeared to be higher than that of the interferon alfa-2a group. The incidence of adverse events appeared to be similar in the 135µg and 180µg peginterferon dose groups. The sponsor concluded that the 180 µg peginterferon dose should be tested in the pivotal studies.

The dose of ribavirin chosen for study was 1000 or 1200 mg po daily based on body weight < or ≥ 75 kg. This is the recommended dose for interferon alfa-2b and ribavirin combination therapy. Patients were instructed to take ribavirin with food because of evidence that food increases the bioavailability of ribavirin.

SUMMARY OF STUDY NV15801

Study Title

“A Phase III, Randomized, Multicenter Efficacy and Safety Study Comparing the Combination of Pegylated-Interferon alfa 2a and Ribavirin to REBETRON in the Treatment of Patients with Chronic HCV Infection”

Study Design

Randomized, multicenter, international, partially blinded, active controlled (REBETRON) phase 3 study of two Peginterferon alfa 2a regimens in 1149 treatment naïve patients with histologically, serologically and virologically documented chronic hepatitis C. Subjects were randomly assigned to one of three treatment arms: Peginterferon alfa 2a monotherapy, peginterferon alfa 2a combined with ribavirin, or Intron A/Rebetol on a 1:2:2 basis. Subjects were treated for 48 weeks and were followed for 24 weeks.

Dosing

- Peginterferon alfa-2a (Roche): 180 µg in 1 mL solution administered sc once weekly in combination with Ribavirin (COPEGUS, Roche): 200 mg/tablet, 1000 - 1200 mg administered po daily in split doses. The dose of COPEGUS and REBETOL was based upon body weight, patients <75 kg received 1000mg per day and those >75 kg received 1200 mg per day.

- REBETRON: Interferon alfa-2b (Intron A, Schering): 3 MIU in 0.5 mL solution administered sc three times per week in combination with Ribavirin (REBETOL Schering/ICN): 200 mg/capsule: 1000 - 1200 mg administered po daily in split doses based upon body weight.

- Placebo: Identical-appearing, equivalent numbers of tablets as ribavirin (Roche) administered po daily in split doses for use in the monotherapy arm.

Dosing Modification Rules

Ribavirin

The dose adjustment guidelines for ribavirin were the same across study groups. Ribavirin was to be reduced to 600 mg per day if (1) a patient without significant cardiovascular disease experienced a fall in hemoglobin to <10 g/dL and >8.5 g/dL or (2) a patient with stable cardiovascular disease experienced a fall in hemoglobin by >2 g/dL during any 4 weeks of treatment. Once a patient's ribavirin dose was held due to either a lab abnormality or adverse event, the investigator could attempt to increase the dose of ribavirin to 600 mg daily, and further to 800 mg daily. However, it was not recommended that ribavirin be increased to its original assigned dose (1000-1200 mg).

Peginterferon and interferon

If a patient experienced a clinically significant adverse event or a laboratory abnormality, the dose of peginterferon or interferon was lowered to pre-specified levels based on the degree of severity of the event as shown below.

Number of Dose Reduction Levels for Adverse Event or Laboratory Abnormality

Severity

Grade

- Mild
- Moderate Limited
- Moderate Persistent
- Severe Limited
- Severe Persistent
- Life-Threatening

Level

- 0
- 0
- 0 - 1
- 0 - 1
- 1 - 2
- Stop Drug

The table below shows the guidelines for lowering the dose of peginterferon when patients experienced neutropenia or thrombocytopenia.

Dose Adjustments for Low Absolute Neutrophil and Platelet Counts

Parameter	Downward Dose Adjustment
ANC (cells/mm³)	
≥1000	None
750 - 999	Week 1 - 2: Immediate 1 Level adjustment Week 3 - 48: None
500 - 749	Week 1 - 2: Delay or hold dose until ≥750 then resume dose with 1 Level adjustment Week 3 - 48: Immediate 1 Level adjustment
250 - 499	Week 1 - 2: Delay or hold dose until ≥750 then resume dose with 2 Level adjustment Week 3 - 48: Delay or hold dose until ≥750 then resume dose with 1 Level adjustment
<250	Stop Drug
Platelet Count (cells/mm³)	
≥50,000	None
35,000 - 49,000	Delay or hold dose until ≥ 50,000 then resume dose with 1 Level adjustment
25,000 - 34,000	Delay or hold dose until ≥ 50,000 then resume dose with 2 Level adjustment
<25,000	Stop Drug

The dose of interferon was to be reduced to 1.5 MIU tiw if a patient experienced a fall in white blood count to $<1.5 \times 10^9/l$ (but $>1.0 \times 10^9/l$) or a fall in neutrophil count to $<.75 \times 10^9/l$ (but $>.5 \times 10^9/l$) or a platelet count to $<50 \times 10^9/l$ (but $>25 \times 10^9/l$)

Dose Reduction Levels for Peginterferon alfa-2a and Interferon alfa-2b

	Assigned Dose	Dose Reduction Levels		
Peginterferon alfa-2a	180 ig	135 ig	90 ig	45 ig
Interferon alfa-2b	3×10^6	2.2×10^6	1.5×10^6	----

If four or more consecutive doses of test drug were held or otherwise not administered (i.e. the patient had not received test medication for more than 28 days), the patient was considered intolerant of the test medication or non-compliant.

Study Population

Men and women outpatients \geq 18 years of age with serologically and histologically proven CHC, elevated ALT, and detectable HCV RNA. Excluded were patients with HIV, other forms of hepatitis, a history of severe psychiatric or cardiac disease, severe seizure disorders, severe retinopathy, or previous interferon or ribavirin therapy.

Primary Efficacy Outcome

The primary outcome was a combined endpoint of non-detectable serum HCV-RNA (<100 copies/ml by a commercial PCR assay) and normal serum ALT activity after the 24-week treatment-free follow-up period (nominally 72 weeks).

Secondary Efficacy Outcomes

The following were the principal secondary outcomes:

- End-of-treatment virologic and biochemical responses
- Sustained virological and biochemical responses
- End-of-follow-up histological changes from pretreatment.

Withdrawal for Treatment Failure

In both studies, study subjects who did not demonstrate either a virologic response (HCV negative or $\geq 2 \log_{10}$ decrease) or a biochemical response(normal ALT) could be withdrawn from the study by 12 weeks of therapy and were to be withdrawn from study if unresponsiveness persisted by 24 weeks.

Clinical and Laboratory Evaluations

One certified laboratory performed all HCV RNA PCR determinations. Local laboratories could be used for repeat testing required for safety assessments. Patients were assessed for safety at weeks 1, 2, 4, 6 and 8 and then every 4 weeks during treatment and follow-up. Patients who were prematurely withdrawn from treatment were followed for 12 weeks after treatment. Following the initiation of treatment, quantitative viral titers were also obtained at weeks 4, 12 and 24 only if the qualitative titer was positive. Qualitative titers (AMPLICOR) were obtained at weeks 4, 12, 24, 48, 60 and 72. Serum ALT activities were obtained by the same schedule for safety assessments. The liver biopsy at baseline and week 72 was reviewed by one pathologist.

Statistical Analyses

Primary efficacy analysis

- The primary efficacy population was the Intention to Treat population which was defined as all subjects randomized.
- This study analyzed categorical variables using the Cochran-Mantel-Haenszel test. Stratification variables were country and pretreatment HCV genotype. Breslow- Day's test was used to test the homogeneity of the odds ratio across the strata formed by country and genotype.

- A “closed testing procedure” was planned to allow for all 3 possible pairwise comparisons. First, the global hypothesis of no treatment differences would be tested at a significance level of 0.05. Next, if the global hypothesis was rejected, the three pairwise treatment comparisons among the three treatment groups would be tested at a significance level of 0.05. In addition to hypothesis testing, two-sided 97.5% confidence intervals of odds ratio would be provided.
- Interim analysis: A blinded review of all available week 4 PCR data was conducted after 815 patients had been randomized, it was decided to increase the sample size to 450:450:225 (REBETRON:PEG-IFN plus ribavirin:PEG-IFN plus placebo) for a total 1125 in order to detect a 10% improvement (instead of the 12% planned originally) of PEG-IFN plus ribavirin over REBETRON with at least 80% power. Sustained response rates of 40%:50%:40% were assumed in the calculation. The power to reach statistical significance between PEG-IFN plus ribavirin and PEG-IFN plus placebo was estimated to be 68% with the increased sample size.

MAJOR PROTOCOL AMENDMENTS

Amendment D: Three hundred additional patients were added to protocol to ensure that the study could detect a statistically significant treatment difference of at least 10% improvement of PEG-IFN plus ribavirin over REBETRON. This decision was based on a blinded interim analysis of week 4 virological data. The total study population was raised to 1125 and the 1:2:2 randomization was retained. A liver biopsy at 48 weeks in a portion of patients was added (50 in each arm) to evaluate safety issues. The week 12 discontinuation policy for non-responders was made optional in light of literature reports of success with 24 weeks.

Amendment E, G: Previously, 150 patients (13% of total) were scheduled to have an end of treatment biopsy. To increase concordance with other studies, the numbers and timing of liver biopsies were changed to 225 patients or 20% at end of follow-up. Twenty patients treated with Rebetron□ would have end-of-treatment liver biopsies.

Amendment H: The definition of sustained virologic response was two consecutive HCV RNA measurements \leq 21 days apart measured \leq 408 days with the lower limit of week 60. To be considered a responder, a patient had to have normal serum ALT activity and no detectable virus at the end of untreated-follow-up period

STUDY RESULTS

Study Centers

There were 81 participating study centers in US, Europe, Australia, Taiwan, Mexico, and Brazil. Differences in treatment response between geographic regions have been observed in studies of interferon therapies. These differences are attributable at least in part to differences in the distribution of baseline demographic and disease factors that predict response to treatment. For this reason the distribution of baseline variables, the treatment responses, and the safety data were analyzed by subdividing the study

population into U.S., non-US, Europe, and “Other”. The centers in the US contributed 41% of the patients participating in the study.

Patient Disposition

1149 patients were randomized; 28 patients were randomized but did not receive any treatment. The two comparison arms had equivalent numbers of individuals randomized but untreated. **Table 3** shows that somewhat fewer subjects in the PEG-IFN monotherapy and IFN-alfa 2b+ ribavirin arms completed 48 weeks of treatment compared to the PEG-IFN +ribavirin arm (67% versus 76%). This difference was due to higher numbers of subjects withdrawn from the protocol for futility at 24 weeks in those two arms. The remainder of the withdrawals from the protocol were mostly for adverse events or laboratory abnormalities (See review of safety).

Table 3. Disposition of Patients

	PEG-IFN alfa-2a N (%)	PEG-IFN alfa-2a+ Ribavirin N (%)	IFN alfa-2b + Ribavirin N (%)
Randomized	227	465	457
Treated	224 (99)	453 (97)	444 (97)
Completed: 12 wks of treatment	217 (96)	435 (94)	426 (93)
24 wks of treatment	197 (87)	414 (89)	402 (88)
48 wks of treatment	152 (67)	353 (76)	304 (67)
24 wks of follow-up	146 (64)	334 (72)	290 (63)

Patient Demographics

The mean age of study participants was approximately 43 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. There was no upper age limit but very few elderly patients were enrolled. The mean weight of participants was approximately 79 kg in all three arms with the recorded range from 42 to 156 kg. The subjects enrolled in US centers were on average heavier than subjects enrolled in non-US centers (See **Table 4**). Peginterferon alfa-2a and interferon alfa-2b were administered as fixed doses and the ribavirin was crudely weight-adjusted based on body weight above or below 75 kg. Given the wide range in body weights of study subjects, the differences in body weight between subjects in US and Non-US centers, and the fixed or crude weight-adjusted dosing, the analysis of safety and efficacy by body weight would be an important review objective.

Approximately 2/3 of the participants were men. This gender distribution is consistent with the higher prevalence of HCV in men. Approximately 84% of participants were Caucasian. Overall 5% of participants were black, (11% of US participants). Approximately 5% of participants both in the total population and in the US sites were Hispanic. 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. Response to interferon therapy is lower in African Americans and in Hispanics for reasons not fully understood. It should be noted that the sponsor has already

undertaken studies to assess the safety and efficacy of peginterferon alfa-2a and ribavirin combination therapy in patients from these ethnic groups.

Table 4 summarizes the patient demographics in the treated population. US patients weigh more, have somewhat higher body mass index and are also older compared to Non-Us patients.

Table 4. Population Baseline Characteristics by Geographic Region^a

Factor	All Patients N %	U.S. N %	Non-U.S. N %	Europe N %	Other N %
	1121 ^b (100) ^c	460 (41)	661 (59)	451 (40)	210 (19)
Age (years)					
<35	268 (23)	50 (11)	209 (32)	154 (34)	55 (26)
35-44	405 (36)	185 (40)	220 (33)	142 (31)	78 (37)
45-54	329 (29)	187 (41)	142 (21)	89 (20)	53 (25)
55-64	108 (10)	32 (7)	76 (11)	55 (12)	21 (10)
>65	16 (1)	3 (1)	13 (2)	10 (2)	3 (1)
Gender					
Male	800 (71)	333 (72)	467 (71)	314 (70)	153 (73)
Female	321 (29)	127 (28)	194 (29)	137 (30)	57 (27)
Ethnic Group					
White	943 (84)	385 (84)	558 (84)	436 (97)	122 (58)
Black	53 (5)	48 (11)	5 (1)	3 (1)	2 (1)
Asian	64 (6)	3 (1)	61 (10)	9 (1)	52 (25)
Other	61 (5)	24 (5)	37 (6)	3 (1)	34 (16)
Body Mass Index					
≤25	577 (51)	222 (48)	355 (54)	265 (59)	90 (43)
>25	543 (49)	238 (52)	305 (46)	185 (41)	120 (57)
Weight (kg)					
<64	75 (16)		175 (26)	127 (28)	48 (23)
<74	316 (28)	112 (24)	204 (31)	142 (31)	52 (26)
75-<85	274 (24)	121 (26)	153 (21)	102 (23)	51 (25)
85-98	230 (21)	111 (24)	129 (20)	80 (18)	49 (25)
>98	116 (14)	116 (25)	0	0	0

^a Analysis group: Treated patients

The demographic characteristics were reasonably well distributed across the treatment groups (not shown).

Disease Characteristics at Baseline

Source of HCV Infection

The means of acquisition of HCV infection was similar across treatment groups (**Table 5**). The predominant mode of transmission was injection drug use. The second highest source of HCV in participants was sporadic or unknown and the third most common was transfused blood products.

Table 5. Infection Source and HCV Genotype

		PEG-IFN alfa-2a N = 227	
N	%	PEG-IFN alfa-2a Ribavirin 1000-1200mg N = 465	
N	%	IFN alfa-2b Ribavirin 1000-1200mg N = 457	
N	%		
Infection Source			
Injection drug use		82 (36)	197 (42)
Transfusion		182 (40)	47 (21)
Unknown		87 (19)	101 (22)
		72 (32)	134 (29)
		127 (28)	

Viral Genotype, Viral Load and Severity of Liver Disease at Baseline

Approximately two thirds of participants in the study were infected with genotype 1 (Table 6); the number was somewhat higher in US study patients compared to non-US patients (see Table 7). The distribution of genotype 1 observed in the study patients is consistent with the incidence of this genotype in HCV infected patients in the US population. Among the non-genotype 1, only types 2 and 3 were significantly represented in the study. The proportion of patients with high viral load was evenly distributed across the three study arms for the entire population and in geographic subgroups. No

relationship has been established between the rate of disease progression or severity of liver disease and the HCV genotype or the number of circulating HCV-RNA copies. Both viral genotype and viral load predict response to interferon treatment, however, with high viral load genotype 1 having the least likelihood of response to interferon treatment.

Table 6. HCV Genotypes by Treatment Group

	PEG-IFN alfa-2a N = 227		PEG-IFN alfa-2a Ribavirin 1000-1200mg N = 465		IFN alfa-2b Ribavirin 1000- 1200mg N = 457	
	N	%	N	%	N	%
Genotype						
Type 1	146	(64)	305	(66)	292	(64)
1a	70	(31)	143	(31)	158	(35)
1b	69	(30)	160	(34)	124	(27)
Other	7	(3)	2	(0)	10	(2)
Non-1	81	(36)	160	(34)	165	(36)
2	37	(16)	56	(12)	62	(14)
3	34	(15)	88	(19)	85	(19)
4	9	(4)	13	(3)	12	(3)
5	1	(<1)	-	-	4	(1)
6		-	2	(<1)	1	(<1)

It is also established that patients with cirrhosis have a lower likelihood of responding to interferon therapy. The proportion of patients who had cirrhosis at baseline was numerically similar across the study arms with 25 (17%) of PEG-IFN monotherapy, 40 (13%) of PEG-IFN/ribavirin and 32 or (11%) of the Interferon alfa-2b/ribavirin having histologic evidence of cirrhosis at baseline. The incidence of cirrhosis was numerically lower in Non-US centers (Europe in particular) compared to the US centers (**Table7**).

Table 7. Baseline Disease Characteristics by Geographic Region^a

Factor	All Patients		U.S.		Non-U.S.		Europe		Other	
	N	%	N	%	N	%	N	%	N	%
	1121 ^b (100) ^c		460 (41)		661 (59)		451 (40)		210 (19)	
HCV RNA										
<2x10 ⁶	378 (34)		147 (32)		231 (35)		153 (34)		78 (37)	
>2x10 ⁶	740 (66)		310 (68)		430 (65)		298 (66)		132 (63)	
Genotype										
1	728 (65)		322 (70)		406 (61)		268 (59)		138 (66)	
Non-1	393 (35)		138 (30)		255 (39)		183 (41)		72 (34)	
Histology										
Cirrhosis	144 (13)		72 (16)		72 (11)		37 (8)		35 (17)	
No Cirrhosis	977 (87)		388 (84)		589 (89)		414 (92)		175 (83)	

^a Analysis group: Treated patients

Primary Efficacy Analysis

The primary comparison in this study was between PEG-IFN alfa 2a plus ribavirin and IFN alfa 2b plus ribavirin. The purpose of the PEG-IFN monotherapy arm was to provide information on the impact of ribavirin on both efficacy and safety when used in combination with PEG-IFN. The intent to treat population was used for the efficacy analysis and was defined as all subjects randomized whether or not they received treatment.

The primary endpoint in this study was the combined sustained (24-weeks post-treatment) virologic and biochemical response. **Table 8** shows a numerical difference (6%) that favors peginterferon alfa-2a and ribavirin over interferon alfa-2b and ribavirin. The p value for the difference was 0.057. Peginterferon alfa-2a and ribavirin combination therapy was superior to peginterferon alfa-2a monotherapy.

Table 8. Sustained Virologic and Biochemical Response at 24 wks Post-treatment¹

	PEG-IFN alfa-2a ----- N = 227 Group(a)	PEG-IFN alfa-2a ribavirin N = 465 Group(b)	IFN alfa-2b ribavirin N = 457 Group(c)
Sustained Virologic and Biochemical Response	55 (24%)	210 (45%)	180 (39%)
Pairwise comparisons²	Odds ratio		P
b vs. c	1.30 (0.95, 1.78)		0.057
b vs. a	2.70 (1.79, 4.10)		0.001
c vs. a	2.08 (1.37, 3.16)		0.001

¹Intent- to-treat population

²Global test of treatment difference: P<0.001

Secondary Efficacy Analyses

Table 9 shows a secondary efficacy analysis using sustained virologic response at 24 weeks post treatment. In this analysis, the treatment difference between PEG-IFN alfa 2a plus ribavirin and IFN-alfa-2b plus ribavirin is 8% and this difference does achieve statistical significance. Both regimens performed better than the PEG-IFN monotherapy which was consistent with expectations. There is a good concordance between biochemical and virologic response. However in a few patients who achieved a sustained virologic response, transaminase levels had not returned to normal by endpoint. The possibility exists that in some of these cases the ALT elevation might be unrelated to CHC.

Table 9. Sustained Virologic Response at 24 wks Post-treatment¹

	PEG-IFN alfa-2a ----- N = 227 Group (a)	PEG-IFN alfa-2a ribavirin N = 465 Group (b)	IFN alfa-2b ribavirin N = 457 Group (c)
Sustained Virologic Response	62 (27%)	234 (50%)	190 (42%)
Pairwise comparisons²	Odds ratios		P
b vs. c	1.49 (1.09, 2.05)		0.004
b vs. a	2.92 (1.94, 4.41)		0.001
c vs. a	1.94 (1.29, 2.92)		0.001

¹Intent- to-treat population

²Global test of treatment difference: P<0.001

Other secondary endpoint consider virologic and biochemical response at either the end of follow-up (72 wks) or at the end of therapy (48 wks) and are shown in **Table 10**. These endpoints provided evidence in support of the superiority of peginterferon alfa-2a and ribavirin, over interferon alfa-2b and ribavirin.

Table 10. Other Secondary Efficacy Analyses¹

	Peg-IFN alfa 2a ---- N=227	Peg-IFN alfa 2a ribavirin N=465	IFN-alfa 2b ribavirin N=457
Sustained Biochemical Response (WK 72)	72 (32%)	233 (50%) OR: 1.37 (1.01, 1.87)	197 (43%)
End-of-Treatment Virologic Response (WK 48)	132 (58%)	314 (68%) OR: 2.16 (1.58, 2.97)	231 (51%)
End-of-Treatment Biochemical Response (WK 48)	91 (40%)	249 (54%) OR: 1.30 (0.96, 1.77)	217(47%)

¹Intent-to-treat population

OR: Odds ratios PEG-IFN/R vs. IFN/R

Efficacy endpoints for pivotal trials of interferon-based therapies for CHC have evolved with the advent of validated assays for HCV RNA. The first interferon therapies were licensed based on demonstration of normalization of serum transaminase levels (biochemical response) supported by improvement in liver histology. Subsequently biochemical response combined with loss of detection of HCV RNA (virologic response) became a standard primary efficacy outcome. The agency's current thinking is that virologic response alone is appropriate as a primary efficacy endpoint. The Anti-Viral Drugs Advisory Committee on December 12, 2001, endorsed the use of a sustained virologic response 24 weeks after the completion of treatment. While the p value for the pre-specified primary endpoint comparing PEGASYS and COPEGUS with REBETRON was 0.057 , a number of secondary endpoints including virologic response alone or biochemical response alone provided strong support for the superiority of peginterferon alfa-2a and ribavirin over interferon alfa-2b and ribavirin.

Finally, changes in liver histopathology in response to treatment were evaluated in a subset of patients. A liver biopsy with histology consistent with chronic hepatitis C within 12 months of enrollment was required for enrollment in the study. Paired liver biopsies were obtained after treatment in approximately 20% of patients. Response to treatment based on Histologic Activity Score was defined as ≥ 2 point decrease in score from baseline. Over 70% of patients in all treatment groups were observed to have a modest reduction in inflammation compared to baseline (**Table 11**). Approximately 20% of patients had no change in inflammation score and 3-5% had an increase in inflammation score.

When histologic response is compared to sustained viral response it would appear that those patients who had a sustained virologic response are more likely to have a histologic response. Overall, the number of subjects with paired biopsies is small, the improvement

in histology from baseline is modest and there are no statistically significant differences between the treatment groups.

Table 11. Histologic Responders in Patients with Paired Biopsies

	Peg-IFN alfa 2a ---- N=39	Peg-IFN alfa 2a ribavirin N=80	IFN-alfa 2b ribavirin N=79
Responders	28/39 (72%)	64/80 (80%)	60/79 (76%)

SUBGROUP ANALYSES

Subgroup Analysis: Patients who Relapse in the Post-treatment Period

Patients with HCV RNA negative at the end of treatment but positive at the end of follow-up (24 weeks post-treatment) were considered to have relapsed. The proportion of patients who relapsed (positive or missing HCV-RNA) was highest in the PEG-IFN monotherapy group. As for the two combination therapy groups, the relapse rate in the PEG-IFN alfa 2a/ribavirin group was higher than in the IFN alfa 2b/ribavirin group (see **Table 12**). It should also be noted that the end of treatment response rate of the PEG-IFN alfa 2a/ ribavirin group was higher than that of the IFN-alfa 2b/ribavirin group.

Table 12. Relapse in Patients with Undetectable HCV-RNA at End of Treatment ¹

	PEG-IFN alfa 2a ---- N= 227	PEG-IFN alfa 2a ribavirin N=465	IFN-alfa 2b ribavirin N=457
Responder at end-of-treatment (48 wks)	132 (58%)	314 (68%)	231 (51%)
Responder at end-of-follow up (24 wks post-treatment)	60 (26%)	221 (47%)	181 (40%)
Relapsers	72/132 (55%)	93/314 (30%)	50/231 (22%)

¹Intent-to-treat population

Subgroup Analysis: Time to First Loss of HCV RNA in Treatment Responders

The majority of individuals who ultimately achieve a sustained virologic response have negative HCV-RNA at 12 weeks of therapy. Those proportions were 75% in the PEG-IFN monotherapy group, 84% in the PEG-IFN/ribavirin group and 78% in the IFN/ribavirin group. By 24 weeks, those numbers had increased to 91% in the PEG-IFN monotherapy group, and 95% in the two combination therapy groups.

The attainment of a negative HCV-RNA at 12 weeks also has predictive value for the success of a subject in achieving a sustained viral response (see **Table 13**). In the PEG-IFN alfa 2a plus ribavirin group, 205 of the 279 patients who were HCV RNA negative at 12 weeks achieved sustained virologic response for a positive predictive value of 73%. On the other side, 134 of 174 patients who ultimately did not achieve sustained virologic response had a positive HCV-RNA at 12 weeks, a 77% negative predictive value. Those same positive and negative predictive values for the IFN-alfa 2b/ ribavirin were similar with a 74% positive predictive value and 82% negative predictive value. In contrast, the

positive predictive value for the monotherapy arm was 54% with a negative predictive value of 88% presumably reflecting the lower efficacy of the monotherapy. This study allowed for continuation of participation beyond 24 weeks for patients who had either evidence of virologic response (negative HCV RNA or $\epsilon 2 \log_{10}$ drop in viral titer) or evidence of a biochemical response (normalization of ALT). Expanding the definition of viral response to include subjects who have a positive HCV RNA but whose viral titer has decreased $\epsilon 2 \log_{10}$ permits even greater negative predictive value. As shown in **Table 14**, of the subjects receiving PEG-IFN alfa 2a/ribavirin only two not meeting this definition ultimately had a sustained viral response for a negative predictive value of 97%.

Table 13. Correlation between In-Treatment and Post-Treatment (≥ 12 weeks) Virologic Response

Treatment Duration		Peg-IFN alfa 2a ---- N= 227		Peg-IFN alfa 2a ribavirin N=465		IFN-alfa 2b ribavirin N=457	
		yes	no	yes	no	yes	no
Week 4	yes	29	12	96	24	63	17
	no	36	147	149	184	135	229
Week 12	yes	49	41	205	74	155	55
	no	16	118	40	134	43	191
Week 24	yes	59	66	232	105	188	76
	no	6	93	13	103	10	170
Week 48	yes	62	66	225	75	185	38
	no	3	93	20	133	13	208

Table 14. Correlation Between Reduction in HCV RNA ≥ 2 log at Week 12 and Sustained^a Response

		Sustained Response	
		yes	no
Week 12 HCV RNA negative or decreased $\epsilon 2$ - log (base 10) from baseline titer	yes	243	147
Sustained Response	no	2	73

^a2 consecutive HCV RNA negative at ≥ 12 wks post-treatment

Subgroup Analysis: Treatment Response by Viral Genotype and Viral Load at Baseline

Patients with viral genotype 1, regardless of viral load, had a lower response rate compared to patients with other genotypes (**Table 15**). Patients with high viral load ($> 2 \times 10^6$ copies of HCV RNA/ml serum) also had lower responses compared to patients with low viral load.

Patients with both genotype 1 and high viral load were least likely to respond both in the PEG-IFN alfa 2a/ribavirin group (39%) and in the IFN/ribavirin group (32%). The influence of viral load appeared to be less in non-genotype 1 patients in the PEG-IFN/ribavirin group.

Table 15. Sustained Virologic Response by HCV Genotype and Viral Titers¹

	Peg-IFN alfa 2a		Peg-IFN alfa 2a ribavirin		IFN-alfa 2b ribavirin	
	N	% Response	N	%Response	N	% Response
ALL PATIENTS	62/227	(27)	234/465	(50)	190/457	(42)
Genotype 1	27/146	(18)	129/305	(42)	100/292	(34)
Genotype non-1	35/81	(43)	105/160	(66)	90/165	(55)
Type 1 –low titer	15/44	(34)	58/114	(51)	39/92	(42)
–high titer	12/101	(12)	71/181	(39)	61/188	(32)
–missing	1	--	10	--	12	--
Non 1 –low titer	15/25	(60)	31/44	(70)	36/56	(64)
–high titer	20/54	(37)	71/108	(66)	54/103	(52)
- missing	2	--	8	--	6	--

¹Intent-to-treat population

Subgroup Analysis: Response to Treatment by Age, Gender, Ethnic Group, Cirrhosis and Geographic Region

The effect of age, gender, ethnicity, cirrhosis on treatment response was examined in the three study groups. The effects were consistent across groups and were also consistent with previous observations (see **Table 16**). The effect of these factors on treatment response was also examined by geographic region and did not yield notable new hypotheses (not shown).

Age

In general, younger patients had higher treatment responses with all three regimens compared to older patients (**Table 16**). The efficacy in US patients was lower than in non-US at most age categories.

Table 16. Virologic Response^a by Age, Gender, Ethnic Group, Cirrhosis, and Geographic Region

		Peg-IFN alfa 2a		Peg-IFN alfa 2a ribavirin		IFN alfa 2b ribavirin	
		N	%SVR	N	%SVR	N	%SVR
All Patients		224	(29)	453	(53)	444	(44)
Age (yrs):	<35	43	(42)	109	(68)	107	(54)
	35-44	91	(31)	154	(56)	165	(47)
	45-54	70	(23)	136	(43)	123	(36)
	55-64	20	(10)	48	(35)	40	(33)
	>65	0		8	(50)	8	(50)
Gender:	Men	151	(33)	324	(53)	325	(43)

	Women	73 (30)	129 (54)	119 (47)
Ethnic Group:	White	186 (29)	372 (54)	385 (46)
	Black	13 (15)	27 (22)	13 (23)
	Asian	12 (75)	28 (82)	24 (54)
	Other	13 (15)	26 (38)	22 (18)
Cirrhosis:	Present	34 (21)	56 (41)	54 (35)
	Not-Present	190 (30)	397 (55)	390 (46)
Geography:	U.S.	93 (26)	184 (42)	183 (36)
	Non-U.S.	131 (31)	269 (61)	261 (50)

^atreated population

Gender:

Overall there was little difference between the SVR rate of men and women in this study.

Racial and Ethnic Background:

Response rates were lower in Black and Hispanic patients compared with the response rate in Caucasians. African Americans made up the vast majority of Black patients enrolled (48/53). The response rate in Asian patients on the other hand was higher than Caucasians. The validity of these observations is somewhat questionable due to the very low numbers of minority patients that were enrolled in this study.

Cirrhosis at Baseline

The unfavorable effect of cirrhosis on treatment response was observed in all three treatment arms. In each arm, individuals with cirrhosis had a 9-14 point lower percentage of viral response. PEG-IFN alfa-2a and ribavirin combination therapy induced higher responses than IFN alfa 2b and ribavirin combination therapy (41% versus 35%). The US versus non-US trends favoring the latter are seen again in these subgroups.

Geographic Region

Roughly 40% of study patients were enrolled in the US; 40% of the other patients were enrolled in Europe, and roughly 20% were enrolled in Australia, Taiwan, Mexico, Brazil. **Table 16** shows that overall the proportion of virologic responders in each of the treatment arms was higher in patients enrolled at non-US centers compared to patients enrolled at US centers. Various prognostic factors were explored to examine this treatment difference. The difference in response was attributable to a higher proportion in US compared to non-US in poor prognostic baseline variables including older age, higher body weight, higher proportion of HCV1 or cirrhosis.

Exploratory analyses were conducted to analyze treatment effect in US and non-US populations in subgroups defined by body weight, genotype, and baseline viral titer. These analyses are provided in **Appendix 1** (see **Tables 17** and **18**). A logistic regression analysis including genotype, viral titer, geographic region, and weight found that the geographic region was not a significant factor contributing to treatment response. Thus, the differences in sustained virological response for the overall population observed between US and non-US patients appear to be largely due to imbalance in other important prognostic factors for response.

SAFETY ANALYSES

Overview of Adverse Events

Nearly all patients experienced one or more adverse events (**Table 19**). The incidence of severe adverse events was similar across groups. Serious adverse events were numerically higher in the peginterferon groups (12%) compared to the interferon/ribavirin group (9%). The incidence of treatment discontinuation for adverse events or laboratory abnormalities was 10-11% in the combination therapy groups and 7% in the peginterferon monotherapy group overall. The incidence of dose modification of the interferon therapy for adverse event or laboratory abnormality was higher for peginterferon (27-32%) compared to interferon (18%). The most common reason for dose modification was neutropenia and/or thrombocytopenia. The incidence of withdrawal from treatment was not different between the interferon combination arms. Also, the incidence of treatment discontinuation or modification was not different in the US centers compared to non-US centers. The higher rates of SAEs and dose modification suggest the potential for greater toxicity of PEG-IFN and ribavirin compared to IFN and ribavirin.

~~Taken together the serious adverse events and the treatment discontinuation and dose modification data suggest the potential for greater toxicity of peginterferon/ribavirin compared to interferon/ribavirin.~~

Table 19. Overview of Adverse Events

	Peg-IFN alfa 2a		Peg-IFN alfa 2a ribavirin		IFN alfa 2b ribavirin	
	N	%	N	%	N	%
Adverse Events:	Any severity	212 (95)	446 (99)		435 (98)	
	Severe	63 (28)	131 (29)		127 (29)	
	Serious	26 (12)	53 (12)		38 (9)	
	Death	2	0		1	
Withdrawals^a	15 (7)	44 (10)		47 (11)		
Dose modification^a:	PEG-IFN or IFN	61 (27)	145 (32)		81 (18)	
	Ribavirin	---	181 (40)		164 (37)	

^adue to adverse event or laboratory abnormality

Most Common Adverse Events

The incidence of new adverse events was summarized for the treatment period, the post-treatment period and the treatment and post-treatment periods combined

Table 20 shows that the incidence of the most common adverse events for the treatment plus post-treatment period was not higher in the peginterferon/ribavirin group compared to the interferon/ribavirin group.

Most Commonly Affected Body Systems

The most common adverse event was a systemic reaction consisting of fatigue/weakness/asthenia with or without headache, fever, chills/rigors. The second most common group of adverse events was neuropsychiatric with irritability, insomnia, impaired concentration/memory impairment, depression, anxiety/nervousness. The musculoskeletal system was commonly affected with myalgias and arthralgia. GI manifestations were also prominent (nausea, vomiting, anorexia, weight loss, abdominal pain, diarrhea). Finally skin manifestations included alopecia, dermatitis, pruritus, and injection site reactions.

Table 20. Common Adverse Events: In-Treatment and 24 Weeks Post-treatment ^a

ADVERSE EVENT	PEG-IFN alfa-2a	PEG-IFN alfa-2a ribavirin	IFN alfa-2b ribavirin
	N = 223 No. (%)	N = 451 No. (%)	N = 443 No. (%)
Fatigue	98 (44)	242 (54)	244 (55)
Headache	115 (52)	211 (47)	230 (52)
Pyrexia	85 (38)	195 (43)	247 (56)
Myalgia	94 (42)	189 (42)	220 (50)
Insomnia	52 (23)	168 (37)	174 (39)
Nausea	58 (26)	130 (29)	145 (33)
Alopecia	48 (22)	128 (28)	151 (34)
Rigors	52 (23)	106 (24)	157 (35)
Arthralgia	64 (29)	121 (27)	112 (25)
Irritability	56 (25)	109 (24)	123 (28)
Depression	44 (20)	95 (21)	131 (30)
Pruritus	41 (18)	101 (22)	88 (20)
Appetite decreased	24 (11)	96 (21)	98 (22)
Dermatitis	29 (13)	95 (21)	80 (18)
Diarrhoea	54 (24)	77 (17)	68 (15)
Dizziness	31 (14)	81 (18)	70 (16)
Asthenia	26 (12)	69 (15)	72 (16)
Dyspnoea	20 (9)	70 (16)	72 (16)
Cough	23 (10)	73 (16)	51 (12)
Dry skin	20 (9)	50 (11)	64 (14)
Anxiety	18 (8)	51 (11)	60 (14)
Back pain	29 (13)	52 (12)	46 (10)
Abdominal pain upper	35 (16)	41 (9)	50 (11)
Injection site inflammation	26 (12)	56 (12)	44 (10)
Concentration impairment	28 (13)	41 (9)	53 (12)
Vomiting	17 (8)	52 (12)	51 (12)
Weight decrease	18 (8)	52 (12)	49 (11)
Abdominal pain	28 (13)	44 (10)	34 (8)
Sore throat	18 (8)	42 (9)	30 (7)
Dry mouth	14 (6)	33 (7)	37 (8)
Pain	14 (6)	36 (8)	30 (7)
Dyspepsia	9 (5)	35 (8)	30 (7)
Sinusitis	12 (5)	35 (8)	23 (5)
Nasopharyngitis	17 (8)	28 (6)	20 (5)
Sweating increased	10 (4)	30 (7)	23 (5)
Constipation	4 (2)	24 (5)	33 (7)
Dyspnoea exertional	8 (4)	22 (5)	31 (7)
URI	13 (6)	23 (5)	25 (6)
Influenza	18 (8)	18 (4)	22 (5)
Herpes simplex	15 (7)	22 (5)	20 (5)
Weakness	10 (4)	24 (5)	23 (5)
Eczema	3 (1)	30 (7)	23 (5)
Hypothyroidism	14(6)	19 (4)	23 (5)
Anorexia	7 (3)	21 (5)	24 (5)
Mouth ulceration	4 (2)	22 (5)	25 (6)
Vision blurred	11(5)	25 (6)	15 (3)
Memory impairment	12(5)	20 (4)	16 (4)
Nervousness	6(3)	17 (4)	23 (5)
Rash erythematous	12(5)	18 (4)	14 (3)
Tooth abscess	9(4)	23 (5)	12 (3)

^aincidence \geq 5%, listed in descending order

Serious Adverse Events

Deaths

There were 3 deaths occurring in patients participating in this study, none of which occurred during treatment. Two deaths occurred during the post treatment follow-up period. The third death occurred approximately a year after treatment was stopped, was caused by a hepatoma that first became manifest near the end of her treatment program. Screening CT scans at study enrollment and 6 months into treatment had failed to detect this mass. Of the other two deaths, one also in the monotherapy arm was a drowning associated with a motor vehicle accident. There was no concern that this represented a suicide. The final death occurred in an IFN combination arm patient who withdrew early from study because of irritability. His death occurred approximately 2 months after study withdrawal and was unobserved. Autopsy findings revealed cocaine cross reactives and 280 ng/mL of benzoylecognine but no free cocaine or cocaethylene in the blood. Autopsy findings of note were limited to the cardiovascular system. There was bilateral ventricular enlargement with left ventricular dilatation and hypertrophy. It was judged that his death was caused by hypertensive heart disease rather than cocaine overdose because of the lack of free cocaine in his system.

Individual SAEs

Individual serious adverse events were rare (<1%) and were primarily infectious, neuropsychiatric, gastrointestinal, inflammatory and hematologic disorders (see **Table 21**). Serious infections will be discussed separately. Serious neuropsychiatric disorders occurred in all three study arms and included depression, bipolar disorder, psychosis, suicide attempt, addiction relapse, fatigue, trigeminal neuralgia. Abdominal pain without identified cause occurred in all three arms as well as events suggestive of subjects' underlying liver disease such as hemorrhoidal bleeding and hematemesis. Inflammatory or rheumatologic serious adverse events such as thyroiditis, pericarditis, arthralgias, new onset psoriasis, interstitial pneumonitis, polyarthritis, sarcoidosis occurred in all three arms but to a somewhat greater extent in the PEG-IFN arms. There were sporadic cases likely caused by ischemic or inflammatory mechanisms related to the interferons such as optic neuritis, retinal hemorrhage, and myocardial ischemia.

Table 21. Serious Adverse Events by Body System

	PEG-IFN alfa 2a ---- N= 227		PEG-IFN alfa 2a ribavirin N=465		IFN-alfa 2b ribavirin N=457	
	N	%	N	%	N	%
Neuro-Psychiatric	4	2	14	3	15	3
Infection	7	3	16	3	8	2
Gastrointestinal	3	1	7	2	7	2
Endocrine	2	1	2	<1	1	<1
Ophthalmic	0	0	2	<1	1	<1
Cardiac	1	<1	4	1	2	<1
Pulmonary	1	<1	4	1	2	<1
Skin rash	1	<1	0	0	1	<1
Neoplasms	4	2	2	<1	2	<1
Rheumatologic	1	<1	3	1	1	<1
Trauma	2	1	3	1	1	<1
Anaphylaxis	1	<1	0	0	0	0

Vascular	1	<1	1	<1	2	<1
Neutropenia	0	0	1	<1	0	0
Thrombocytopenia	1	<1	0	0	0	0
Anemia	0	0	2	<1	0	0
Fever/weakness	1	<1	3	1	0	0
Totals	30	13	63	14	42	9

Numbers represent individual patients who may have more than one category of serious adverse event

Serious Infections

Infections were more common in both PEG-IFN arms than in the IFN alfa 2b combination therapy arm. Bacterial causes, either proven or empirically treated predominated and where a causative organism was recovered it was likely part of the patient's normal bacterial flora. ~~it was likely part of the patient's normal bacterial flora~~ The most likely explanation for apparent impairment of normal host resistance in this setting would be the neutropenia commonly caused by interferon therapy.

As shown in **Table 22**, grade 4 neutropenia (<500 ANC) was detected in a case of amoebiasis in the PEG-IFN monotherapy arm and in a case of epiglottitis caused by *Staphylococcus aureus* in the PEG-IFN combination arm. These may not be the only instances of a severe neutropenia playing a role in these serious infections since as is also seen in **Table 22**, there is often a significant time interval both before and after the onset of a serious infection when the neutrophil count is not recorded. Both of the two cases where grade 4 neutropenia is detected are unusual for the timeliness of the leukocyte sampling. Even when neutropenia is not documented, expected neutrophil response to serious infection often appears to be blunted. It is possible that sampling delays may be playing a role in this observation but this blunting is seen predominantly with the PEG-IFN arms and is not seen to the same extent in the IFN/ribavirin arm.

Significant and severe lymphopenia is much more common, especially in the 16 patients with serious infections in the PEG-IFN ribavirin combination arm. Of these 16 individuals, 10 had lymphocyte counts recorded below 1000. The significance of this lymphopenia to the subject's serious infection is not known since most of the affected individuals appeared to be exhibiting either a bacterial infection or an inflammatory non-infectious entity.

Table 22 Serious Infections and Corresponding CBC, Nadir PMN, Lymphocyte[

Diagnosis	Onset Day	Resolved Day	Last CBC Prior/day	First CBC After/day	PMN * Nadir	Lymphs* Nadir
Peg-IFN 180µg monotherapy						
Cellulitis(antibiotics)						
Cervicitis(no antibiotic)						
Viral Infection						
Diarrhea-Pseudomonas						
Cellulitis-S. Aureus						
Viral pneumonia						
Amoebiasis						
Cellulitis(antibiotic)						
Otitis externa(psoriatic-antibiotic)						
Otitis externa						
Pneumonia-S. pneumoniae						
Skin abscess-streptococcus						
Bronchiectasis(no antibiotic)						
UTI(E. coli)						
Pyrexia(antibiotic)						

Sinusitis-Rx antibiotics						
Septic arthritis(S. aureus)						
Pneumonia-interstitial						
Neurosyphilis						
Epiglottis-S.aureus						
Appendicitis						
Abdominal Abscess(E.coli)						
Gastroenteritis(no antibiotics)						
LRTI(antibiotics given)						
Appendicitis(antibiotics)						
Skin abscess(antibiotics)						
Appendicitis(antibiotics)						
Biliary peritonitis(antibiotics)						
Gastroenteritis						
Pyelonephritis(E. coli)						
Pneumonia(antibiotics)						

Withdrawal from Treatment because of Adverse Events or Laboratory Abnormalities

A similar proportion of patients withdrew from treatment for clinical adverse events and laboratory abnormalities in each of the combination therapy treatment groups (10% and 11%), whereas fewer patients withdrew from PEG-IFN alfa-2a monotherapy for these reasons (7%). Most adverse events and laboratory abnormalities were successfully managed with dose reduction and therefore did not require withdrawal of the patient .

The most common types of events leading to discontinuation were psychiatric disorders (mainly depression-related events), especially in the combination therapy groups. The highest proportion of patients discontinuing due to psychiatric events was in the IFN alfa-2b plus ribavirin group (PEG-IFN alfa-2a monotherapy, 1%; PEG-IFN alfa-2a plus ribavirin, 3%; IFN alfa-2b plus ribavirin, 4%). Other events leading to withdrawal only in the combination groups and not in the monotherapy group include thyroid disorders (8 patients), anemia, and dyspnea (both 3 patients), suggesting a possible causal or aggravating role of ribavirin in these events. More patients in the PEG-IFN alfa-2a plus ribavirin group withdrew for hematologic abnormalities (2%) than in the other groups (both 1%), with thrombocytopenia and neutropenia being the most frequent abnormalities leading to withdrawal. All other types of events leading to discontinuation occurred in ≤1% of patients in each treatment arm.

Table 23 Withdrawals for Laboratory Abnormalities/ AE Treated Population

WD-Reason	Peg-IFN alfa 2a ---- N= 223	Peg-IFN alfa 2a ribavirin N=451	IFN-alfa 2b ribavirin N=443
Patient numbers	15(7%)	44(10%)	47(11%)
LAB	2	11	10
Neutropenia	1	2	2
Thrombocytopenia	1	3	
Anemia		1	2
Liver Assoc Abn		2	
Thyroid Abnorm		3	6
AE	13	33	37
General	1	4	5

Psychiatric	3	12	18
Infections		2	
GI/ABD Pain	2	1	1
Endocrine			1
DERM/Alopecia	2	3	5
Neurologic	1	2	1
Musculo-skel/Rheu	1	4	1
Ophthalmologic	1	2	1
Trauma			
Poss Hypersensitive	1		1
Pulm/Card/CP		1	
DVT			1
Cancer	1	1	2
Sarcoidosis			
Other		1	
TOTAL	15	44	

Adverse Events Leading to Permanent Discontinuation or Modification of Treatment

In the peginterferon alfa-2a and interferon alfa-2b combination therapy groups the main adverse events that led to treatment discontinuation were neuropsychiatric disorders (3%) including suicide attempt, depression, fatigue, anxiety. The second most common causes were bone marrow toxicity/hemolysis (2%) with neutropenia, thrombocytopenia, pancytopenia, and anemia. Rarer causes ($\leq 1\%$) included the following: dermatitis, arthritis, colitis, and endocrine/metabolic disorders such as autoimmune thyroiditis (with hypo- or hyper-thyroidism), hypertriglyceridemia, exacerbation of diabetes mellitus (ketoacidosis, retinopathy).

The incidence of adverse events that led to modification of interferon dosage was higher in the combination therapy groups (11%) compared to the monotherapy group (6%). The incidence of all adverse events that led to modification of ribavirin dosage was similar (17-22%) across the three study groups (see **Table 24**).

Laboratory Abnormalities Leading to Permanent Discontinuation or Modification of Treatment

Very few individuals were withdrawn for neutropenia, thrombocytopenia or anemia. The incidence of clinically significant laboratory abnormalities that led to modification of peginterferon dosage was 3-fold higher (24-25%) in the patients receiving PEG-IFN compared to patients receiving IFN (8%). The incidence of lab abnormalities leading to modification of ribavirin dosage was lowest in the peginterferon /placebo ribavirin group (4%), intermediate in the interferon/ribavirin group (19%) and highest in the peginterferon/ribavirin group (24%). Bone marrow ~~toxicity~~-toxicity (neutropenia, thrombocytopenia) was the principal cause for modification of interferon dose and was several-fold higher in patients receiving peginterferon compared to interferon (see **Table 24**). Anemia was the main cause of dose modification of ribavirin (approximately 20%) in patients receiving PEG-IFN or IFN plus ribavirin.

Table 24. Adverse Events and laboratory Abnormalities Leading To Dose Modification

	PEG-IFN alfa-2a N %	Ribavirin Placebo N %	PEG-IFN alfa-2a N %	Ribavirin N %	IFN alfa-2b N %	Ribavirin N %
AE or Lab abnormal	61 (27)	46 (21)	145 (32)	181 (40)	81 (18)	164 (37)
AE	14(6)	39 (17)	48 (11)	95 (21)	47 (11)	97 (22)
Lab abnormality	54 (24)	9(4)	111 (25)	108 (24)	36 (8)	84 (19)
ALT	1(<1)	0	2(<1)	1(<1)	1(<1)	0
Anemia	0	8 (4)	4 (1)	99 (22)	13 (3)	83 (19)
Neutropenia	38 (17)	0	91 (20)	6 (1)	24 (5)	1 (<1)
Thrombocytopenia	14 (6)	1 (<1)	18 (4)	2 (<1)	1 (<1)	0
Other Lab abnorm	1(<1)	0	4 (1)	2(<1)	2(<1)	1(<1)

Analysis of the impact of dose modification of PEG-IFN upon treatment response using cumulative dose calculations demonstrates a proportional relationship with lower overall treatment response associated with lower cumulative doses of PEG-IFN in both the monotherapy and combination therapy arms.

Table 25. Sustained SVR as a Function of Cumulative Dose of PEG-IFN Monotherapy or PEG-IFN Combined with Ribavirin

Cumulative PEG-IFN alfa-2a Dose	PEG-IFN alfa-2a + Ribavirin Placebo	PEG-IFN alfa-2a + Ribavirin
N ^a	215	424
<4590 µg	2/36 (6%)	3/58 (5%)
4590 µg to <6840 µg	7/45 (16%)	21/46 (46%)
6840 µg to <8640 µg	12/34 (35%)	54/85 (64%)
ε 8640 µg	44/100 (44%)	167/235 (71%)
Total	65/215 (30%)	245/424 (58%)

Laboratory data:

Neutropenia

Median neutrophil counts decreased from baseline values in all three treatment groups, with the largest decreases occurring during the first 2 weeks of treatment. Median neutrophil counts then stabilized, remaining at around 45% of baseline in the two PEG-IFN alfa-2a groups and around 60% of baseline in the IFN alfa-2b group during the remainder of the 48-week treatment period. Median neutrophil counts increased following the end of treatment, returning to normal values by week 52 and reaching baseline levels by week 72 (see **Figure 1**).

Figure 1
Median Neutrophil Counts during Treatment and 24 weeks post Treatment

Nearly 50% of subjects in the PEG-IFN arms experienced Grade 3 or higher neutropenia during treatment or in follow-up. By comparison, less than 25% of subjects in the IFN-alfa 2b combination arms experienced that level of neutropenia (see **Table 26**). The impact that this level of neutropenia had on infections appears to have been small in this study.

Table 26. Lowest Neutrophil Counts During Treatment and Post-treatment

	Normal >2 ^a		Grade 1 1.5-1.99		Grade 2 1.0-1.49		Grade 3 0.5-0.99		Grade 4 <0.5	
	N	%	N	%	N	%	N	%	N	%
PEG-IFN alfa-2a	13	(5.8)	25	(11.2)	96	(43.0)	81	(36.3)	8	(3.6)
PEG-IFN alfa-2a ribavirin	22	(4.9)	37	(8.2)	165	(36.7)	205	(45.6)	21	(4.7)
IFNalfa-2b	69	(15.6)	105	(23.8)	169	(38.2)	94	(21.3)	5	(1.1)

^acounts x10⁹/L

Thrombocytopenia

Median platelet counts remained close to baseline levels throughout treatment in the IFN alfa-2b plus ribavirin arm. Median platelet counts decreased progressively during the first 8 weeks of treatment in the PEG-IFN alfa-2a monotherapy and PEG-IFN alfa-2a plus ribavirin treatment groups, stabilizing at about 55% of baseline levels in the PEG-IFN alfa-2a plus monotherapy group and approximately 70% of baseline values in the PEG-IFN alfa-2a plus ribavirin group. Median platelet counts normalized by 4 weeks post-treatment and had recovered to baseline levels by week 72 (see **Figure 2**).

Figure 2

Patients receiving peginterferon with or without ribavirin had a two- to three-fold higher incidence of thrombocytopenia and were more likely (5% vs. 0.2%) to reach grade 3 thrombocytopenia defined as counts between 20,000 and 50,000/mm³ (see **Table 27**) There were no episodes of significant bleeding attributable to the thrombocytopenia associated with the PEG-IFN treatment.

Table 27. Lowest Platelet Counts During Treatment and Post-treatment

	Normal	Grade 1	Grade 2	Grade 3	Grade 4
	>100 ^a	75<100	50 <75	20<50	<20
	N %	N %	N %	N %	N %
PEG-IFN alfa-2a	108 (48)^b	65 (29)	36 (16)	14 (6)	0
PEG-IFN alfa-2a ribavirin	303 (67)	80 (17)	45 (10)	22 (4)	0
IFN alfa-2b	388 (88)	36 (8)	17 (4)	1 (0.2)	0

^acountsx10⁹/L

Anemia

The median hemoglobin concentration decreased in all treatment groups during the first 8 weeks of treatment. The decrease was similar in the PEG-IFN alfa-2a plus ribavirin and IFN alfa-2b plus ribavirin groups, with the median hemoglobin concentration stabilizing at approximately 12.5 g/dL from a baseline of approximately 15 g/dL. The decrease in

the PEG-IFN alfa-2a monotherapy arm was less marked (stabilizing at around 14 g/dL). Median hemoglobin concentrations returned to baseline levels within 8 weeks post-treatment in all treatment groups (not shown).

Approximately 10% of patients receiving PEG-IFN or IFN plus ribavirin experienced drops in hemoglobin to levels below 10g/dl compared to 3% in the peginterferon monotherapy group (**Table 28**). Two percent of patients in the peginterferon ribavirin group reached hemoglobin levels < 8.5 g. The maximum drop was 9.5g.

Table 28. Lowest Hemoglobin Levels During Treatment and Post-treatment

	8.5 <10 g/dl N %	< 8.5 g/dl N %
PEG-IFN alfa-2a	7 (3.1)	1 (0.4)
PEG-IFN alfa-2a ribavirin	40 (9)	9 (2)
IFN alfa-2b	47 (11)	1 (0.2)

Exploratory Analysis: The effect of BMI upon occurrence of hematologic toxicity

As has been previously mentioned, the interferons are administered as a fixed dosage in this study. The ribavirin is weight crudely weight adjusted above and below 75kg. There is a suggestion that efficacy is affected by body weight. An exploratory analysis was undertaken to examine the effect of Body Mass Index (BMI) upon the incidence of the four most frequently encountered hematologic effects adverse effects with interferon therapy: Hemoglobin < 10, Grade 4 Neutropenia, Grade 3 /4 Neutropenia, and Grade 3 /4 thrombocytopenia.

As demonstrated in **Table 29**, significant anemia (hemoglobin <10) was seen more frequently in subjects with BMI <25 than in those with BMI ≥ 25 in all three study arms, approximately 4% greater incidence in the lower BMI. This same trend is seen in Grade 3/ 4 neutropenia although when Grade 4 Neutropenia is isolated, the greater incidence in the lower BMI is only seen in the PEG-IFN combination arm. With thrombocytopenia, the only significant difference is in the PEG-IFN monotherapy arm and then it occurs in the opposite direction, the greater incidence is in larger BMI patients.

Table 29 Occurrence of Hemoglobin <10, Grade 4 Neutropenia, Grade 3/ 4 Neutropenia, and Grade 3/ 4 Thrombocytopenia in Patients Categorized by BMI

	PEG-IFN alfa 2a ---- N= 227		PEG-IFN alfa 2a ribavirin N=465		IFN-alfa 2b ribavirin N=457	
	BMI < 25 N=102 %	BMI ≥ 25 N=122 %	BMI < 25 N=174 %	BMI ≥ 25 N=279 %	BMI < 25 N=199 %	BMI ≥ 25 N=245 %
Hemoglobin <10	6	2	14	9	13	9
Grade 3/ 4 Neutropenia	43	37	52	49	25	20
Grade 4 Neutropenia	3	4	7	3	1	2

Grade 3/4 Thrombocytopenia	4	8	5	5	0	0.4
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Dose Modification for Specific Thresholds Across Treatment Groups and Geographic Regions

The incidence of dose modification of ribavirin for severe anemia (not shown) were similar in the two combination therapy groups and were appropriately lower in the monotherapy group. It could not be determined how consistently protocol-required dose-modifications were applied across geographic regions. Median decreases in hemoglobin, were greater in the non-US centers versus the US centers.

Immunogenicity of Interferon

The presence of antibodies to interferon was measured comparing baseline and week 56 testing. A total of 14 patients (4.8%) in the Peg-IFN combination arm developed neutralizing anti-interferon antibodies ranging in titer from 117 to 2600 interferon neutralizing units per milliliter (INU/mL) Anti-interferon neutralizing antibodies were detected in 3 patients(1.1%) of the IFN-alfa 2b plus ribavirin group and 3 patients(2.3%) in the monotherapy group. It should be noted that the assay for neutralizing antibodies to the IFN-alfa 2b is not validated. The immunogenicity of PEG-IFN in combination with ribavirin requires further study.

The development of neutralizing antibodies did not preclude achieving a sustained virologic response. Of the 14 individuals detected in the PEG-IFN combination arm to have interferon neutralizing antibodies, 9 achieved a sustained virologic response. In addition, 2/3 monotherapy patients and 1/3 IFN alfa 2b/ribavirin combination patients also achieved a sustained virological response (**Table 30**)

Table 30. Development of anti-interferon antibodies

	PEG-IFN alfa-2a	PEG-IFN alfa-2a + ribavirin	IFN alfa-2b + ribavirin
Patients with antibodies	3/132 (2.3%)	14/294 (4.8%)	3/270 (1%).
Virologic responders	2/3 (66%)	9/14 (64%)	1/3 (33%)

Safety in Patients with Cirrhosis

A higher proportion of cirrhotic patients withdrew from therapy in the combination treatment arms (9% and 11%) than in the PEG-IFN alfa-2a monotherapy arm (6%) The proportion was similar to that seen in the overall safety population. Reasons for withdrawal included hematologic abnormalities (anemia and thrombocytopenia) and psychiatric events.

As in the overall safety population, a higher proportion of cirrhotic patients required modification of their interferon dose for clinical adverse events and laboratory abnormalities in the PEG-IFN alfa-2a monotherapy and combination therapy arms than in the IFN alfa-2b plus ribavirin arm. Cirrhotic patients were more likely than noncirrhotic patients to require modification of their interferon dose in all treatment groups. In the PEG-IFN alfa-2a groups, this difference was mainly due to dose modifications for laboratory abnormalities, in particular, dose reductions for thrombocytopenia (21% for cirrhotics vs. 6% for the overall population in the monotherapy group and 16% for cirrhotics vs. 4% for the overall population in the combination group). Dose reductions

for neutropenia in the two PEG-IFN alfa-2a groups were similar in cirrhotic patients and in the overall population. In contrast, in the IFN alfa-2b plus ribavirin group, the difference between cirrhotic patients and the overall population was mainly the result of dose reductions for clinical adverse events (19% for cirrhotics vs 11% for the overall population).

CONCLUSIONS

Efficacy

Peginterferon alfa-2a (180 ig once weekly SC) in combination with ribavirin (1000/1200 mg po daily in split doses taken with food) is superior to interferon alfa-2b (3×10^6 three times weekly SC) in combination with ribavirin (1000/1200 mg po daily in split doses taken with food).

The treatment difference is an absolute 6-8% as shown by sustained viral response, biochemical response, and combined viral and biochemical response at 12-24 weeks after the end of 48 weeks of therapy.

HCV genotype 1, high ($>2 \times 10^6$ /ml) circulating HCV RNA titers, presence of cirrhosis, older age, African American origin, higher body weight are associated with lower response. The effect of body weight on treatment response may be confounded by other prognostic factors.

Response rates were lower in patients enrolled in US centers compared to non-US centers. Lower response was attributable to higher incidence in US compared to non-US in baseline variables (older age, higher body weight, higher proportion with HCV1 or cirrhosis) that predict poorer response to treatment. Response rates appeared to be lower in patients with higher body weights.

Peginterferon alfa-2a and ribavirin combination therapy is superior to peginterferon alfa-2a monotherapy. The treatment difference is approximately 20% absolute.

Safety

Compared to interferon alfa-2b combination therapy, peginterferon alfa-2a combination therapy is associated with slightly higher incidence of overall serious adverse events (12% vs. 9%) serious infections (4% vs. 2%), grade 4 neutropenia (5% vs. 1%) and grade 3 thrombocytopenia (5% vs. 0.2) and higher requirement of dose modification (32% vs. 18%). There was no difference in premature withdrawals between combination treatment groups (10% vs. 11%). There was a suggestion of an effect of body weight on toxicity.

Risk/benefit

The 6-8% higher response rate with peginterferon combination therapy compared to interferon combination therapy should be weighed against the risk of higher toxicity (in particular bone marrow) of peginterferon. Given the effect of body weight on treatment response and toxicity, and the lack of dose ranging studies of combination therapy, studies of the safety and efficacy of lower doses of peginterferon may be needed. Given the effect of body weight on treatment response, studies of efficacy and safety of weight-based dosing compared to fixed dosing should be considered.

SUMMARY OF STUDY NV 15942**Study Title**

“A phase III, randomized, multicenter, efficacy and safety study examining the effects of the duration of treatment and the daily dose of ribavirin in patients with chronic hepatitis C virus infection treated with the combination of peginterferon alfa-2a and ribavirin.”

Study Objective

The goal was to determine the optimal duration of combination therapy as well as the optimal dose of ribavirin for the combination.

Study Design

Randomized, multicenter, international, double blinded phase 3 study evaluating the safety and efficacy of four PEG-IFN alfa 2a and ribavirin regimens. Subjects were randomly assigned to one of the four treatment arms. All participants were given the same dose of PEG-IFN-180µg sc q week. In the first two arms, PEG-IFN alfa 2a was administered with either 800mg or 1000-1200mg of ribavirin for 24 weeks. In the remaining two arms PEG-IFN alfa 2a was administered with either 800mg or 1000-1200mg of ribavirin for 48 weeks. A 24- week treatment free follow-up was part of the design for all 4 study arms. Patients in the first two study arms were not informed of the 24 week duration of therapy prior to reaching that point to minimize bias.

Patients were randomized and assigned to each of the study arms on the basis of HCV viral genotype and viral titer. In the original protocol it was stated that within each geographic region, patients with genotype non-1 and low viral load, genotype non-1 and high viral load and genotype 1 and low viral load would be randomized in a ratio of 1:2:1:2 to treatment groups A:B:C:D. Patients with genotype 1 and high viral load would be randomized in a ratio of 1:1:3:3 to treatment groups A:B:C:D. This was subsequently changed to 1:1:5:5 because of inability to recruit low viral titer genotype non-1.

Dosing

Peg-IFN alfa 2a: 180µg in 1 ml solution administered sc once weekly for either 24 weeks or 48 weeks.

Ribavirin: 200mg tablets, between 800 and 1200 mg administered daily in split doses. The ribavirin was administered with an identical appearing placebo tablet as specified by study arm to make up the appropriate daily dosage taken with food

Placebo: Identical appearing to the ribavirin tablet, administered as specified in the study arm in split dose.

Ribavirin Dose Modification

Ribavirin would be reduced to 600 mg per day the following occurred: (1) a patient *without* significant cardiovascular disease experienced a fall in hemoglobin to <10 g/dL and >8.5 g/dL or (2) a patient *with* stable cardiovascular disease experienced a fall in hemoglobin by >2 g/dL during any 4 weeks of treatment.

Moreover, ribavirin would be discontinued under the following circumstances:
a patient without significant cardiovascular disease experienced a fall in Hgb to less than 8.5g/dl; a patient with stable cardiovascular disease maintains a Hgb <12g/dl despite 4 weeks on reduced dose. If ribavirin was discontinued, it could be reintroduced at the investigators' discretion at a daily dose of 600mg

PEG-IFN Dose Modifications

The general dose guidelines and dose adjustments for low absolute neutrophil and platelet counts were the same for this study as the previous one.

Assigned Dose	One Level Adjustment	Two Level Adjustment	Three Level Adjustment
PEG-IFN 180 µg	PEG-IFN 135 µg	PEG-IFN 90 µg	PEG-IFN 45 µg

Once a patient's unit dose had been decreased, the investigator could attempt to increase the dose back to or toward that which was originally assigned if the following conditions were satisfied: the event or circumstance responsible for the dosage adjustment had resolved or improved; the patient had been at the lower dose for ≤4 consecutive doses; ≤6 total doses had been administered to the patient at the lower level during the entirety of the treatment period.

Study population

Men and women ≥ 18 years of age with serologically and histologically proven CHC, elevated ALT, and detectable HCV RNA. Excluded were patients with HIV, other forms of hepatitis, a history of severe psychiatric or cardiac disease, severe seizure disorders, or severe retinopathy, or previous interferon or ribavirin therapy.

Primary Efficacy Outcome:

The primary measure of efficacy was a combined endpoint of both sustained biochemical and virological response calculated as the number of patients with both a sustained biochemical and virological response divided by the number of patients who were randomized.

Prior to database closure the sponsor specified a new primary endpoint: which was non-detectable serum HCV-RNA (<100 copies/ml) at the end of the 24 week treatment-free follow-up period.

Primary efficacy analysis population. Intent-to-treat analysis population was defined to include all patients randomized and treated (received at least one dose of study medication).

Secondary Efficacy Outcomes

The following were the principal secondary endpoints:

Sustained virological and biochemical response rates
End-of treatment virological and biochemical responses
Maintenance of virologic and biochemical response after the end of treatment
Histology of liver biopsy: a cross tabulation of the pretreatment and posttreatment histological diagnosis from the blinded review will be provided.

Withdrawal for Treatment Failure

In this study, subjects who did not demonstrate either a virologic response (HCV-PCR negative or $\epsilon 2 \log_{10}$ decrease in circulating virions) or normalization of ALT could be withdrawn from the study at 24 weeks.

Clinical and laboratory evaluations

One certified laboratory performed all HCV RNA PCR determinations. Local laboratories could be used for repeat testing required for safety assessments.

Statistical analyses

Primary efficacy analysis

- Treatment duration and different ribavirin doses were analyzed using the Cochran-Mantel-Haenszel test. Mantel-Haenszel test was stratified by combination of (region, HCV genotype, viral load, and ribavirin dose). Breslow-Day test was performed to assess the homogeneity of the odds ratios over the strata formed by the combination of (region, genotype, viral load, and ribavirin dose). If the p-value from the Breslow-Day test was > 0.2 then data from all patients was used in the primary comparison of treatment duration.
- The primary efficacy population was the Intention-to-Treat population which was defined as the number of subjects randomized.
- The Cochran-Mantel-Haenszel test stratified by geographical region, genotype, viral load, and ribavirin dose would be used to compare the combined sustained response rate between the 24-week and the 48-week treatment group. The Cochran-Mantel-Haenszel test stratified by geographical region, genotype, viral load, and treatment duration would be used to compare the combined sustained response rate between the ribavirin 800 mg and the 1000-1200 mg dose group.
- End-of Treatment virological and biochemical responses, maintenance of virological and biochemical responses and histological responses in the four treatment groups were analyzed using descriptive statistics.

MAJOR PROTOCOL AMENDMENTS

Amendment B:

Because of difficulties in recruiting patients with genotype non-1, low viral titer, this amendment allowed for an increased number of genotype 1, high viral titer to all study arms but with a preponderance in the 48 week duration as before. Within each geographic region, with the exception of the genotype 1, high viral load stratum, patients were randomized in a ratio of 1:1:1:1 to treatment groups A:B:C:D. Patients with genotype 1 and high viral load were randomized in a ratio of 1:1:5:5 to treatment groups A:B:C:D.

Amendment C:

A sustained virological response was defined as two consecutive negative HCV-RNA assessments ε21 days apart at the end of the 24-week untreated follow-up period

A sustained biochemical response was defined as two consecutive normal serum ALT assessments ε21 days apart at the end of the 24-week untreated follow-up period

An end-of-treatment virological response was defined as a negative HCV-RNA assessment at the end of the treatment period.

An end-of-treatment biochemical response was defined as two consecutive normal serum ALT assessments ε21 days apart at the end of the treatment period.

Amendment F:

Primary efficacy analysis population. Intent-to-treat analysis population was defined to include all patients randomized and treated (received at least one dose of study medication).

New primary endpoint: Endpoint of non-detectable serum HCV-RNA (<100 copies/ml) at the end of the 24 week treatment-free follow-up period.

STUDY RESULTS

Study Centers:

There were 99centers in the in US, Europe, Australia, Canada, New Zealand, Taiwan, and Brazil. In the first study, differences in treatment response between geographic regions were observed. These differences were attributed at least in part to differences in the distribution of baseline demographic and disease characteristic factors that predict response to treatment. The distribution of baseline variables, the treatment response and safety data were analyzed by subdividing the study population into U.S., Non-U.S., Europe, and Other for the remainder of the participating sites. In this study the U.S. contributed 34% of the patients participating in the study.

Patient Disposition

In the study 1311 patients were randomized, 27 were randomized but did not receive any treatment and these were distributed equally across all four study arms (see **Table 31**).

The percentage of participants who completed treatment for 24 weeks (the therapy stopping point for Arms A and B) was at or near 90% in all four arms. The percentage of individuals who finished 48 weeks of therapy in Arms C and D was lower at 67 and 72% respectively. This decline in the study population occurred due to withdrawals for futility (which did not occur before 24 weeks) in addition to the greater number of withdrawals for adverse event or laboratory abnormalities (see safety review). In this protocol there was a strong attempt to collect 24 week follow-up data on individuals who withdrew from study because of adverse events and laboratory abnormalities hence the slightly greater numbers in follow-up compared to end of treatment in the two 48 week arms.

Table 31. Disposition of Patients

	24 weeks	48 weeks
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	PEG-IFN Ribavirin 800mg		PEG-IFN Ribavirin 1000/1200 mg		PEG-IFN Ribavirin 800mg		PEG-IFN Ribavirin 1000/1200 mg	
	N	%	N	%	N	%	N	%
Randomized	214		288		365		444	
Treated	207 (97)		280 (97)		361 (99)		436 (98)	
Completed: 12 wks of treatment	198 (93)		269 (93)		353 (97)		421 (95)	
24 wks of treatment	193 (90)		258 (90)		326 (89)		399 (90)	
48 wks of treatment	-----		-----		244 (67)		319 (72)	
24 wks of follow-up	191 (89)		251 (87)		255 (70)		325 (73)	

Patient Demographics

The median age of study participants was 41-42 years of age. The study excluded pediatric patients. There was no upper age limit but very few elderly patients were enrolled. The mean weight of participants was approximately 77 kg in all four arms with the recorded weight range from 41 to 150 kg. As in the previous study, there were notable differences in body weight by geographic region. Compared to Non-US patients, US patients again tended to be older, and heavier than non-US matched subjects, and had higher Body Mass Index (see **Table 32**). The interferons in this study as in the earlier study were given at a fixed dose. The ribavirin was either given at a fixed reduced dose or crudely adjusted on body weight above or below 75kg so that these weight differences may have resulted in a wide range of exposures to both study drugs.

Approximately 2/3 of the participants were men which again is consistent with the higher prevalence of HCV in men. Approximately 89% of the participants were Caucasians. Approximately 3% of the participants were black and even in the US the percentage of African Americans was only 5%. Hispanics made up approximately 1% and the remaining 7% or so were Asians.

Table 32. Population Baseline Characteristics by Geographic Region

Factor	All Patients N %	U.S. N %	Non-U.S. N %	Europe N %	Other N %
	1284 (100)	441 (34)	843 (66)	573 (45)	270 (21)
Age (years)					
35	299 (23)	40 (9)	259 (31)	184 (32)	75 (28)
35-44	476 (37)	172 (39)	304 (36)	195 (34)	109 (40)
45-54	361 (28)	184 (42)	177 (21)	116 (20)	61 (23)
55-64	125 (10)	36 (8)	89 (11)	65 (11)	24 (9)
>65	21 (2)	8 (2)	13 (2)	12 (2)	1 (1)
Gender					
Male	838 (65)	277 (63)	561 (67)	385 (67)	176 (65)
Female	446 (35)	164 (37)	282 (33)	188 (33)	94 (35)
Ethnic Group					
White	1146 (89)	404 (92)	742 (88)	542 (95)	200 (74)
Black	38 (3)	21 (5)	17 (2)	9 (2)	8 (3)
Asian	87 (7)	7 (2)	80 (9)	21 (4)	59 (22)
Other	13 (1%)	9 (2)	4 (1)	1 (1)	3 (1)
Body Mass Index					
≤25	578 (45)	113 (26)	465 (55)	337 (59)	145 (54)
>25	705 (55)	328 (74)	377 (45)	235 (41)	128 (46)
Weight (kg)					
<64	218 (17)		218 (26)	147 (26)	82 (30)

<74	363 (28)	135 (31)	228 (27)	160 (28)	63 (23)
75-<85	313 (24)	100 (23)	213 (25)	147 (26)	67 (25)
85-98	309 (24)	126 (29)	183 (22)	118 (21)	41 (15)
>98	80 (6)	80 (18)			

Disease Characteristics at Baseline

Source of HCV Infection

The source of HCV infection was similar across treatment arms and closely resembled the population in study NV15801 previously discussed. The predominant mode of transmission was injection drug use. The second highest source was sporadic or unknown and the third most common was transfused blood products (see **Table 33**).

Table 33. Source of HCV Infection, Intent-to-Treat Population

Infection Source	Treatment Group			
	PEG-IFN Ribavirin 800mg	PEG-IFN Ribavirin 1000/1200 mg	PEG-IFN Ribavirin 800mg	PEG-IFN Ribavirin 1000/1200 mg
Injection drug use	74 (36%)	96 (34%)	124 (34%)	163 (37%)
Transfusion	39 (19%)	45 (16%)	67 (19%)	80 (18%)
Unknown	72 (35%)	97 (35%)	127 (35%)	131 (30%)

Viral Genotype, Viral Load and Severity of Liver Disease at Baseline

By design, the overall proportion of genotype 1 was slightly lower in this population at 58% versus 65% in study NV 15801. Among the non-genotype 1, only genotypes 2 and 3 were significantly represented. There were only 36 individuals infected with genotype 4. Genotypes 5 and 6 had fewer than 10 individuals each participating in the study (see **Table 34**).

Also by design, the proportion of participants with genotype 1 high viral titer was higher in the two 48 week duration studies in the 1:1:5:5 formula mentioned earlier. All other genotypes and viral loads were evenly distributed across all four treatment arms.

Table 34. HCV Genotype, Intent-to-Treat population

Genotype	PEG-IFN Ribavirin 800mg		PEG-IFN Ribavirin 1000/1200 mg		PEG-IFN Ribavirin 800mg		PEG-IFN Ribavirin 1000/1200 mg	
	Type 1	101	49%	118	42%	250	69%	271
1a	46	22%	54	19%	117	32%	124	28%
1b	55	27%	64	23%	132	37%	147	34%
Other	0	0%	0	0%	1	<1%	0	0%
Non-1	106	51%	162	58%	111	31%	165	38%
2	39	19%	53	19%	46	13%	66	15%
3	57	28%	91	33%	53	15%	87	20%
4	5	2%	12	4%	8	2%	11	3%
5	2	<1%	4	1%	0	0%	1	<1%

6 3 1% 2 <1% 4 1% 0 0%

As in the previous study there were geographic differences in the population demographics. US patients had slightly higher proportion of subjects with genotype 1 compared to non-US sites 61% versus 56%. The proportion of participants with cirrhosis or transition to cirrhosis was higher in US patients versus non-US 29% versus 23% (see **Table 35**).

Table 35. Population Disease Characteristics by Geographic Region, ITT

Factor	Total N %	U.S. N %	Non-U.S. N %	Europe N %	Other N %
All Patients	1284 (100)	441 (34)	843 (66)	573 (45)	270 (21)
HCV Load					
<2x10 ⁶	465 (36)	153 (35)	312 (37)	215 (38)	97 (36)
>2x10 ⁶	819 (64)	288 (65)	531 (63)	358 (62)	173 (64)
Genotype					
1	740 (58)	270 (61)	470 (56)	323 (56)	147 (54)
Non-1	544 (42)	171 (39)	373 (44)	250 (44)	123 (46)
Histology					
Cirrhosis	321 (25)	127 (29)	194 (23)	132 (23)	62 (23)
N/Cirrhosis	963 (75)	314 (71)	649 (77)	441 (77)	208 (77)

Primary Efficacy Analysis

The objectives of this study were to compare (1) 48 with 24 weeks of treatment and (2) 1000 or 1200 mg with 800 mg of ribavirin. As in study NV15801, the original primary efficacy parameter was a combined sustained virological and biochemical response. Amendment F in this protocol permitted the use of sustained virologic response at 24 weeks post treatment as the primary endpoint.

In **Table 36**, using the combined sustained virologic and biochemical response, the odds ratio is 1.26 favoring the longer duration of therapy but the confidence intervals cross 1.00 and the p value is 0.08. The second analysis examines the effect of ribavirin dosage, and here the odds ratio is 1.48, confidence intervals of 1.16-1.89 and a p value of 0.0014 favoring the higher dosage. Pooled analyses of virologic response and of biochemical response also support the longer duration of therapy and higher ribavirin dose.

Table 36. Pooled Analysis of Combined Virologic and Biochemical Response

	Treatment Duration		Ribavirin Dose	
	24 weeks N=487 Group (a)	48 weeks N=797 Group (b)	800mg N=568 Group (c)	1000-1200mg N=716 Group (d)
Hypothesis Tested	48 weeks of therapy is superior to 24 weeks of therapy		1000-1200 mg of Ribavirin is superior to 800mg of Ribavirin	
Pooled Combined Sustained Virologic and Biochemical Response				
Pairwise comparisons	Odds Ratio		P value	
(b) versus (a)	1.26 (0.97, 1.64)		0.080	
(d) versus (c)	1.48 (1.16, 1.89)		0.001	
Pooled Sustained Virologic Response				
(b) versus (a)	1.32 (1.01, 1.73)		0.039	
(d) versus (c)	1.35 (1.05, 1.73)		0.018	

Pooled Sustained Biochemical Response		
(b) versus (a)	1.25 (0.96, 1.62)	0.092
(d) versus (c)	1.51 (1.18, 1.92)	0.001

A comparison of the different treatment regimens in different patient populations defined by genotype and baseline viral titer is presented in **Table 37**. In patients with genotype non-1, irrespective of baseline viral titer, the sustained virologic response was similar after 24 and 48 weeks of treatment. In addition, there was no difference in sustained virologic response between patients receiving 800 mg of ribavirin and patients receiving 1000 or 1200 mg of ribavirin. These results indicate that for patients with genotype non-1, with either a high or a low baseline viral titer, 24 weeks of treatment at a dose of 800 mg of ribavirin is sufficient to obtain the maximum virologic response. The sustained virologic response in the group treated for 24 weeks with 800 mg of ribavirin was 78%. Treatment response in patients with genotype 4, appeared to be highest with 48 weeks of therapy and standard ribavirin dose; the number of patients was too low to draw definitive conclusions.

Among patients with genotype 1, with either high or low baseline viral titers, the sustained virologic response was higher in the 48 week than in the 24 week treatment groups. The sustained virologic response was also higher among patients receiving 1000 or 1200 mg of ribavirin than among patients receiving 800 mg of ribavirin. Thus, in patients with genotype 1, irrespective of baseline viral titer, 48 weeks of treatment with 1000 or 1200 mg of ribavirin resulted in the highest sustained virologic response. With this treatment regimen, 46% of the patients with high viral titer and 60% of the patients with low baseline viral titer achieved a sustained virologic response.

Table 37. Sustained Virologic Response as a Function of Genotype and Baseline Viral Titer

	PEG-IFN/Ribavirin 800 mg x 24 weeks		PEG-IFN/Ribavirin 1000-1200mg x 24 weeks		PEG-IFN/Ribavirin 800mg x 48 Weeks		PEG-IFN/Ribavirin 1000-1200mg x 48 weeks	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR
ALL PATIENTS	112/207	(54)	177/280	(63)	180/361	(50)	259/436	(59)
Genotype 1	29/101	(29)	48/118	(41)	97/250	(39)	136/271	(50)
Low Titer	21/51	(41)	36/71	(51)	31/60	(52)	51/85	(60)
High Titer	8/50	(16)	12/47	(26)	66/90	(35)	85/186	(46)
Genotype Non-1	83/106	(78)	129/162	(80)	88/111	(79)	123/165	(75)
Low Titer	28/39	(72)	48/61	(79)	33/41	(80)	45/57	(79)
High Titer	55/67	(82)	81/101	(80)	50/70	(71)	78/108	(72)
Genotype 2	35/39	(90)	45/53	(83)	40/46	(87)	48/66	(73)
Low Titer	14/14	(100)	9/11	(82)	14/15	(93)	15/19	(79)
High Titer	21/25	(84)	36/42	(86)	26/31	(84)	33/47	(70)
Genotype 3	44/57	(77)	72/91	(79)	37/53	(70)	65/87	(75)
Low Titer	13/20	(65)	30/36	(83)	14/18	(78)	22/29	(76)
High Titer	31/37	(84)	42/55	(76)	23/35	(66)	43/58	(74)
Genotype 4	0/5	(0)	8/12	(67)	5/8	(63)	9/11	(82)
Low Titer	0/4	(0)	8/11	(73)	5/7	(71)	8/9	(89)
High Titer	0/1	(0)	0/1	(0)	0/1	(0)	1/2	(50)
Genotype 5	1/2	(50)	2/4	(50)	0/0	(0)	1/1	(100)
Low Titer	0/0	(0)	0/2	(0)	0/0	(0)	0/0	(0)
High Titer	1/2	(50)	2/2	(100)	0/0	(0)	1/1	(100)
Genotype 6	3/3	(100)	2/2	(100)	1/4	(25)	0/0	(0)

Low Titer	1/1	(100)	1/1	(100)	0/1	(0)	0/0	(0)
High Titer	2/2	(100)	1/1	(100)	1/3	(33)	0/0	(0)

Secondary Efficacy Analyses

Sustained Biochemical Response

Table 38 compares the sustained biochemical response of the different treatment regimens in the patient populations defined by genotype and baseline viral titer. As with the SVR, the SBR supports 48-week/standard-dose ribavirin therapy for genotype 1 in both low and high titer. The SBR also supports 24-week/low-dose ribavirin therapy for genotype non-1 regardless of viral titer.

Table 38. Sustained Biochemical Response as a Function of Genotype and Baseline Viral Titer

	Peg-IFN/Ribavirin 800 mg x 24 weeks N=207		Peg-IFN/Ribavirin 1000-1200mg x 24 weeks N=280		Peg-IFN/Ribavirin 800mg x 48 Weeks N=361		Peg-IFN/Ribavirin 1000-1200mg x 48 weeks N=436	
	N	%SBR	N	%SBR	N	%SBR	N	%SBR
Genotype 1	32/101	(32)	52/118	(44)	96/250	(38)	138/271	(51)
High Titer	12/50	(24)	15/47	(32)	69/190	(36)	88/186	(47)
Low Titer	20/51	(39)	37/71	(52)	27/60	(45)	50/85	(59)
Genotype Non-1	72/106	(68)	119/162	(73)	75/111	(68)	119/165	(72)
High Titer	50/67	(75)	77/101	(76)	49/70	(70)	80/108	(74)
Low Titer	22/39	(56)	42/61	(69)	26/41	(63)	39/57	(68)

Virologic and Biochemical Response at the End of Treatment

In patients with genotype 1, irrespective of baseline viral titer, the virologic response at the end of treatment was higher in the groups treated with 1000/1200 mg of ribavirin compared with those receiving 800 mg of ribavirin. In genotype non-1 patients, the virologic response at the end of treatment was similar in the groups receiving 800 and 1000 /1200 mg of ribavirin.

For both genotype 1 and non-1 patients, the virologic response at the end of treatment seemed to be higher in the 24 than in the 48 week treatment groups, the difference being more pronounced among genotype non-1 patients. This difference is partially due to the fact that a higher percentage of patients in the 48 week treatment groups than in the 24 week treatment groups withdrew from treatment for safety and non-safety reasons and did not have a HCV RNA measurement at the end of treatment (see **Table 39**).

Biochemical responses at the end of treatment were slightly lower than virologic responses at the end of treatment; they followed the same pattern as virologic responses (**Table 40**).

Table 39. Virologic Response at the End of Treatment as a Function of Genotype and Baseline Viral Titer

	PEG-IFN/Ribavirin 800 mg x 24 weeks N=207		PEG-IFN/Ribavirin 1000-1200mg x 24 weeks N=280		PEG-IFN/Ribavirin 800mg x 48 Weeks N=361		PEG-IFN/Ribavirin 1000-1200mg x 48 weeks N=436	
	N	%VR	N	%VR	N	%VR	N	%VR
Genotype 1	69/101	(68)	91/118	(77)	142/250	(57)	177/271	(65)

High Titer	30/50	(60)	31/47	(66)	104/190	(55)	113/186	(61)
Low Titer	39/51	(76)	60/71	(85)	38/60	(63)	64/85	(75)
Genotype Non-1	95/106	(90)	144/162	(89)	72/111	(65)	121/165	(73)
High Titer	63/67	(94)	93/101	(92)	43/70	(61)	78/108	(72)
Low Titer	32/39	(82)	51/61	(84)	29/41	(71)	43/57	(75)

Table 40. Biochemical Response at the End of Treatment

	PEG-IFN/Ribavirin 800 mg x 24 weeks N=207		PEG-IFN/Ribavirin 1000-1200mg x 24 weeks N=280		PEG-IFN/Ribavirin 800mg x 48 Weeks N=361		PEG-IFN/Ribavirin 1000-1200mg x 48 weeks N=436	
	N	%BR	N	%BR	N	%BR	N	%BR
Genotype 1	44/101	(44)	65/118	(55)	109/250	(44)	138/271	(51)
High Titer	19/50	(38)	25/47	(53)	86/190	(45)	90/186	(48)
Low Titer	25/51	(49)	40/71	(56)	23/60	(38)	48/85	(56)
Genotype Non-1	70/106	(66)	108/162	(67)	58/111	(52)	92/165	(56)
High Titer	44/67	(66)	69/101	(67)	36/70	(51)	59/108	(55)
Low Titer	26/39	(67)	39/61	(64)	22/41	(54)	33/57	(58)

Liver Histopathology

The percentages of patients with a histological response were similar in all four treatment groups and ranged from 72% to 78%. The total HAI score with fibrosis decreased in all four treatment groups, and the median change ranged from -3.5 to -4 (**Table 41**). Patients with virologic response had a higher proportion of histologic response than those individuals without a virologic response. The number of patients with paired biopsies was small (approximately 20%).

Table 41. Histologic Responders in Patients with Paired Biopsies

	PEG-IFN/Ribavirin 800 mg x 24 weeks N=48	PEG-IFN/Ribavirin 1000-1200mg x 24 weeks N=51	PEG-IFN/Ribavirin 800mg x 48 Weeks N=68	PEG-IFN/Ribavirin 1000-1200mg x 48 weeks N=93
Responders	35/48 (73%)	40/51(78%)	52/68 (76%)	67/93 (72%)

Subgroup Analyses

Subgroup Analysis: Patients who Relapse in the Post-treatment Period

Patients with undetectable HCV-RNA at the end of treatment but who had detectable HCV-RNA at the end of follow-up were considered to have relapsed. A high percentage of patients with genotype non-1 with either high or low baseline viral titers maintained their end-of-treatment virological response (ε84%). In this patient group, the proportions of patients maintaining their end-of-treatment virological response were similar in the groups treated for 24 and 48 weeks and were also similar in the groups receiving 800 and 1000/1200 mg of ribavirin (see **Tables 42** and **43**).

Among patients infected with genotype 1, irrespective of baseline viral titer, maintenance of the end-of-treatment virological response was affected mostly by treatment duration and to a lesser extent by the dose of ribavirin. The percentage of patients with genotype 1

who relapsed was higher in the 24 week group compared with the 48 week group. The dose of ribavirin affected maintenance of an end-of- treatment virological response in patients with genotype 1 who had high baseline viral titers but not with low baseline titer. In this latter group, there was no significant difference between the higher and lower ribavirin dosages (see **Tables 41** and **42**).

Table 42. Virologic Relapse in Patients with Undetectable HCV-RNA at End of Treatment (24 weeks)

	PEG-IFN /Ribavirin 800 mg x 24 weeks				PEG-IFN/Ribavirin 1000-1200mg x 24 weeks			
	N	EOT/V R	SVR	%Relapse	N	EOT/V R	SVR	%Relapse
Genotype 1	101	69	29	40/69(58)	118	91	47	44/91(48)
High Titer	50	30	8	22/30(78)	47	31	12	19/31(51)
Low Titer	51	39	21	18/39(46)	71	60	35	25/60(42)
GenotypeNon-1	106	95	80	15/80(16)	162	144	127	17/144(12)
High Titer	67	63	54	9/63(14)	101	93	81	12/93(13)
Low Titer	39	32	26	6/32(19)	61	51	46	5/51(10)

Table 43. Virologic Relapse in Patients with Undetectable HCV-RNA at End of Treatment (48 weeks)

	Peg-IFN/Ribavirin 800mg x 48 Weeks				Peg-IFN/Ribavirin 1000-1200mg x 48 weeks			
	N	EOT/V R	SVR	%Relapse	N	EOT/V R	SVR	%Relapse
Genotype 1	250	142	89	53/142(37)	271	177	128	49/177(28)
High Titer	190	104	59	45/104(43)	186	113	79	34/113(30)
Low Titer	60	38	30	8/38(19)	85	64	49	15/64(23)
GenotypeNon-1	111	72	66	6/72(8)	165	121	108	13/121(11)
High Titer	70	43	41	3/43(5)	108	78	67	11/78(14)
Low Titer	41	29	25	4/29(14)	57	43	41	2/43(5)

For end-of treatment biochemical responders the numbers are lower than for the same groups for end-of-treatment virologic responders. The overall pattern of maintenance resembles that of the virological responders (**Tables 44** and **45**). Genotype non-1 maintain their end of treatment response well regardless of which arm they are in. In genotype 1 the 48-week groups have lower relapse compared to 24-week. Ribavirin dose again has its greatest impact on high viral titer genotype 1 and less upon low viral titer. Overall, the biochemical response appears to be less able to distinguish between groups.

Table 44. Biochemical Relapse in Patients with Biochemical Response at End of Treatment (24 weeks)

	Peg-IFN /Ribavirin 800 mg x 24 weeks				Peg-IFN/Ribavirin 1000-1200mg x 24 weeks			
	N	EOT/BR	SBR	%Relapse	N	EOT/BR	SBR	%Relapse

Genotype 1	101	44	20	24/44(55)	118	65	39	26/65(40)
High Titer	50	19	8	11/19(58)	47	25	12	13/25(52)
Low Titer	51	25	12	13/25(52)	71	40	27	13/40(32)
GenotypeNon-1	106	70	56	14/70(20)	162	108	92	16/108(15)
High Titer	67	44	38	6/44(14)	101	69	61	8/69(12)
Low Titer	39	26	18	8/26(31)	61	39	31	8/39(21)

Table 45. Biochemical Relapse in Patients with Biochemical Response at End of Treatment (48 weeks)

	Peg-IFN/Ribavirin 800mg x 48 Weeks				Peg-IFN/Ribavirin 1000-1200mg x 48 weeks			
	N	EOT/BR	SBR	%Relapse	N	EOT/BR	SBR	%Relapse
Genotype 1	250	109	72	37/109(34)	271	138	113	25/138(18)
High Titer	190	86	55	47/86(36)	186	90	74	16/90(18)
Low Titer	60	23	17	6/23(26)	85	48	39	9/48(19)
GenotypeNon-1	111	58	53	5/58(9)	165	92	83	9/92(10)
High Titer	70	36	35	1/36(3)	108	59	52	7/59(12)
Low Titer	41	22	18	4/22(18)	57	33	31	2/33(6)

Subgroup Analysis: Time to First Loss of HCV RNA in Treatment Responders

As in the first study, it was postulated that the majority of individuals who ultimately achieve a sustained virologic response have evidence of virologic response at 12 weeks of therapy. This is the basis for the futility discharge of patients who do not have evidence of a virologic response, defined as either a negative HCV-RNA PCR or ϵ 2 \log_{10} decrease in viral titers. In this study the positive predictive value of all four treatment arms ranged between 60 and 70% for all patients, was considerably higher for genotype non-1, around 80 %, and was lower in genotype 1 (**Table 46**). For genotype 1, the positive predictive value increased from a low of 37% in the low dose ribavirin 24 week group to nearly 60% in the 48 week, high ribavirin dose. The negative predictive value in this study is very high for both genotype 1 and non-1. The futility withdrawal of individuals who failed to achieve a virological response by week 24 somewhat weakens this negative predictive value, but overall it appears valid.

Table 46. Predictive Value of a Virological Response by Week 12 for a Sustained Virological Response as a function of Genotype

GROUP	Early Viral Response	PEG-IFN/Ribavirin 800 mg x 24 weeks N=207		PEG-IFN/Ribavirin 1000-1200mg x 24 weeks N=280		PEG-IFN/Ribavirin 800mg x 48 Weeks N=361		PEG-IFN/Ribavirin 1000-1200mg x 48 weeks N=436	
		SVR	No SVR	SVR	No SVR	SVR	No SVR	SVR	No SVR
All Patients	yes	112	67	177	79	179	129	256	130
	no	0	28	0	24	1	52	3	47
+Predictive Value		112/179=63%		177/256=69%		179/308=58%		256/386=66%	
- Predictive Value		28/28=100%		24/24=100%		52/53=98%		47/50=94%	
Genotype 1	yes	29	49	48	52	96	105	133	94

	no	0	23	0	18	1	48	3	41
+ Predictive Value		29/78=37%		48/100=48%		96/201=48%		133/227=59%	
- Predictive Value		23/23=100%		18/18=100%		48/49=98%		41/44=93%	
Genotype	yes	83	18	129	27	83	24	123	36
	Non-1								
	no	0	5	0	6	0	4	0	6
+ Predictive Value		83/101=82%		129/156=83%		83/107=78%		123/159=77%	
- Predictive Value		5/5=100%		6/6=100%		4/4=100%		6/6=100%	

Subgroup Analysis: Response to Treatment by Age, Gender, and Ethnic Group, and Geographic Region

Age

As in the first study, younger patients had overall higher response rates in all four treatment arms (see **Table 47**).

Table 47. Virologic Response by Age, Gender, Ethnic Group, Cirrhosis, and Geographic Region

	PEG-IFN/Ribavirin 800 mg x 24 weeks		PEG-IFN/Ribavirin 1000-1200mg x 24 weeks		PEG-IFN/Ribavirin 800mg x 48 Weeks		PEG-IFN/Ribavirin 1000-1200mg x 48 weeks	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR
All Patients	207	(52)	280	(62)	361	(50)	436	(61)
Age (yrs):								
<35	52	(71)	69	(71)	86	(57)	92	(66)
35-44	77	(45)	109	(61)	127	(50)	163	(65)
45-54	62	(51)	74	(61)	104	(47)	121	(53)
55-64	14	(57)	19	(47)	34	(29)	53	(60)
>65	4	(25)	2	(50)	10	(30)	7	(43)
Gender:								
Men	140	(50)	185	(62)	226	(50)	287	(56)
Women	67	(55)	95	(63)	135	(50)	149	(69)
Ethnic Group:								
White	183	(55)	254	(63)	315	(51)	394	(61)
Black	7	(29)	9	(22)	11	(45)	11	(64)
Asian	24	(59)	16	(69)	31	(42)	26	(58)
Other	15	(20)	1	(100)	4	(25)	5	(33)
Geography:								
US	69	(48)	94	(57)	121	(46)	157	(52)
Non-US	138	(57)	186	(65)	240	(52)	279	(66)

Gender

Women had somewhat higher response rates in three of the four treatment arms. Treatment response of women varied little at different geographic sites; there was some variability in response by geographic site for men. The role of body weights in this variability was not examined (see **Table 47**).

Ethnic Group

About 90% of the participants in this study were Caucasian. Minority participants were few in number and were not equally distributed across geographic regions making observations regarding their efficacy and regional differences very problematic (see **Table 47**).

Geographic Region

Approximately one third of study patients was enrolled in the U.S., 45% in Europe and 21% from Australia, New Zealand, Taiwan, Canada and Brazil. **Table 47** shows that US patients demonstrate the same trends as the overall group in percentage SVR in each of the treatment arms but consistently at a lower value. The treatment difference between US and non-US ranges from a low of 6% in arm C, (48 weeks/800mg ribavirin) to a high of 14% in arm D, (48 weeks/1000-1200mg ribavirin). The explanations for these differences are the same as discussed in the first study, the somewhat higher percentage of genotype 1 in the US, the older age of the US patients, the higher percentage of patients with cirrhosis or transition to cirrhosis in the US and the heavier weight and higher proportion of obesity as demonstrated by Body Mass Index. Racial differences may play a role as well since the percentage of black patients is highest in the US but the absolute numbers are very similar at 21 versus 17.

Subgroup Analysis. Virologic Response by Body Weight and Geographic Region

For all four treatment groups the greater the patient's baseline weight the lower was the proportion of virologic response (**Tables 48 and 49**). As in the first study, the number of participants in the higher weight groups is greater in the US. The US made up approximately 34% of all the study participants but 50-56% of the individuals >85 kg in each of the study arms.

Table 48. Virologic Response by Body Weight and by Geographic Region (24 week)

	Peg-IFN/Ribavirin 800 mg x 24 weeks						Peg-IFN/Ribavirin 1000-1200mg x 24 weeks					
	Total		US		Non-US		Total		US		Non-US	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR
All BW	207	(52)	69	(48)	138	(57)	280	(62)	94	(57)	186	(65)
BW <64kg	34	(59)	0		34	(59)	45	(67)	0		45	(67)
<74kg	61	(62)	22	(59)	39	(64)	87	(63)	29	(66)	58	(62)
75-85kg	44	(43)	13	(38)	31	(45)	59	(73)	15	(67)	44	(75)
85-98kg	52	(53)	18	(44)	34	(59)	73	(55)	34	(53)	39	(56)
>98kg	16	(44)	16	(44)	0		16	(44)	16	(44)	0	

Table 49. Virologic Response by Body Weight and by Geographic Region (48 week)

	Peg-IFN/Ribavirin 800mg x 48 Weeks				Peg-IFN/Ribavirin 1000-1200mg x 48 weeks			
	N	%SVR	N	%SVR	N	%SVR	N	%SVR

	Total		US		Non-US		Total		US		Non-US	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR
All BW	361	(50)	121	(46)	240	(52)	436	(61)	157	(52)	193	(63)
BW <64kg	66	(48)	0		66	(48)	73	(73)	0		73	(73)
<74kg	102	(54)	37	(49)	65	(57)	113	(65)	47	(62)	66	(67)
75-85kg	86	(45)	30	(47)	56	(45)	124	(56)	42	(45)	83	(62)
85-98kg	86	(52)	33	(45)	53	(57)	98	(57)	41	(51)	57	(61)
>98kg	21	(43)	21	(43)	0		27	(44)	27	(44)	0	

Subgroup Analysis: Virologic Response by Genotype, Viral Load, Cirrhosis and by Geographic Region
Genotype and Viral Load

The response rates by viral genotype and load that are observed in patients in the US are in general consistent with those observed in the overall population (See **Tables 50** and **51**). In certain subgroups (e.g. genotype 1) the response rates demonstrated in the overall population were not observable in the US subgroup.

Table 50. Virologic Response by HCV Genotype, Titer and by Geographic Region (24 weeks)

	Peg-IFN/Ribavirin 800 mg x 24 weeks						Peg-IFN/Ribavirin 1000-1200mg x 24 weeks					
	Total		US		Non-US		Total		US		Non-US	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR
All Subj	207	(52)	69	(48)	138	(57)	280	(62)	94	(57)	186	(65)
Genotyp1	101	(29)	37	(30)	64	(28)	118	(41)	41	(39)	77	(42)
Non-1	106	(78)	32	(69)	74	(82)	162	(78)	53	(72)	109	(82)
Titer:low	90	(54)	29	(52)	61	(56)	132	(63)	42	(64)	90	(62)
high	117	(54)	40	(45)	77	(58)	148	(62)	52	(52)	96	(68)

Table 51. Virologic Response by HCV Genotype, Titer and by Geographic Region (48 weeks)

	Peg-IFN/Ribavirin 800mg x 48 Weeks						Peg-IFN/Ribavirin 1000-1200mg x 48 weeks					
	Total		US		Non-US		Total		US		Non-US	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR	N	%SVR
All Subj	361	(50)	121	(46)	240	(52)	436	(61)	157	(52)	279	(66)
Genotyp1	250	(40)	90	(38)	160	(41)	271	(51)	102	(39)	169	(58)
Non-1	111	(73)	31	(71)	80	(74)	165	(77)	55	(75)	110	(78)
Titer:low	101	(63)	33	(64)	68	(63)	142	(68)	49	(57)	93	(73)
high	260	(45)	88	(40)	172	(47)	294	(59)	108	(53)	186	(62)

Subgroup Analysis Presence of Cirrhosis at Baseline

Cirrhosis is associated with a less favorable treatment response. This study overall had a substantial percentage of patients with cirrhosis (25%). In each treatment arm, individuals with cirrhosis had lower sustained virologic response rates compared to non-cirrhotic participants. This decreased response rate ranged from a low of 9% in the 24 week duration, high ribavirin dose to a high of 21% in the 48 week duration, low dose ribavirin dose arm. As in the overall population, the 48 week duration, high dose ribavirin dose arm had the best sustained virologic response rate for genotype 1 regardless of baseline viral load. With genotype non-1, the higher ribavirin dose arms in each treatment duration pair appeared to do slightly better.

Table 52. Sustained Virological Response in Patients with Cirrhosis or Transition to Cirrhosis

	Peg-IFN/Ribavirin 800 mg x 24 weeks N=44		Peg-IFN/Ribavirin 1000-1200mg x 24 weeks N=71		Peg-IFN/Ribavirin 800mg x 48 Weeks N=91		Peg-IFN/Ribavirin 1000-1200mg x 48 weeks N=115	
	N	%SVR	N	%SVR	N	%SVR	N	%SVR
Genotype 1	6/23	(26)	7/27	(26)	19/67	(28)	32/78	(41)
High Titer	3/14	(21)	1/15	(7)	16/58	(28)	20/57	(35)
Low Titer	3/9	(33)	6/12	(50)	3/9	(33)	12/21	(57)
Genotype Non-1	14/21	(67)	33/44	(75)	15/24	(63)	28/37	(76)
High Titer	12/17	(71)	22/31	(71)	7/14	(50)	20/27	(74)
Low Titer	2/4	(50)	11/13	(85)	8/10	(80)	8/10	(80)

SAFETY ANALYSES

Overview of Adverse Events

Nearly all patients experienced one or more adverse events. The incidence of severe and life-threatening adverse events was higher in the 48-week therapy groups (32%) compared to 24-week therapy groups (22%) (see **Table 53**).

Serious adverse events were numerically lowest in the 24-week therapy/low-ribavirin dose group (3%) and were highest in the 48-week therapy groups (9-10%).

There was one death (drug overdose, in-treatment, judged to be unrelated) in the 24-week therapy/standard-ribavirin dose group and one death (septicemia, in-treatment judged to be possibly related) in the 48-week therapy/low-ribavirin group. In the 48-week/standard-ribavirin group there were two deaths one by suicide (in-treatment judged as probably related) the other caused by drug toxicity occurring 5 months after treatment had been discontinued. Although it was judged by the investigator as unrelated to treatment, it should be noted that the patient developed neuropsychiatric symptoms including depression and ultimately suicidal ideation while on therapy, psychotropic drugs were implicated in his demise and at the time of his demise, he was still on the antidepressants begun while on study.

The incidence of permanent withdrawal for adverse event and laboratory abnormality was lower in the 24-week therapy groups (5%) compared to the 48-week therapy groups (15-16%). The incidence of dose modification of the interferon therapy for adverse event or lab abnormality was somewhat lower in the 24-week therapy groups (26-30%) compared to 48-week therapy groups (33-36%). The incidence of dose modification of the ribavirin therapy for adverse event or lab abnormality was lowest in the 24-week low-ribavirin group (19%) and highest in the 48-week standard-ribavirin group (38%).

Taken together the severe and serious adverse events and the dose-modification data indicate greater toxicity of 48-week therapy compared to 24-week therapy. There is also

a suggestion of potentially higher toxicity of standard ribavirin dose compared to low ribavirin dose.

Table 53. Overview of Adverse Events

	24 weeks		48 weeks	
	PEG-IFN Ribavirin 800 mg	PEG-IFN Ribavirin 1000/1200 mg	PEG-IFN Ribavirin 800 mg	PEG-IFN Ribavirin 1000/1200 mg
Adverse Events:				
Any	200 (97)	275 (98)	355 (98)	27 (98)
Severe	46 (22)	63 (23)	116 (32)	141 (32)
Serious	7 (3)	19 (7)	33 (9)	44 (10)
Deaths	0	1	1	2
Withdrawals^a	10 (5)	13 (5)	59 (16)	67 (15)
Dose Modification^a				
PEG-IFN	63 (30)	73 (26)	120 (33)	159 (36)
Ribavirin	39 (19)	76 (27)	101 (28)	166 (38)

^afor AEs and lab abnormalities

Most Common Adverse Events

Among the most common adverse events were flu-like symptoms such as headache, fatigue, myalgia, pyrexia, rigors, and arthralgia. As expected, psychiatric disorders such as depression, irritability, insomnia, anxiety, and concentration impairment were also frequently reported adverse events. Other common events were gastrointestinal events (nausea, diarrhea, upper abdominal pain, and vomiting), skin disorders (alopecia, pruritus, dermatitis, dry skin, and injection site reactions), respiratory disorders (cough, dyspnea, and sore throat), and metabolic disorders (decreased appetite, anorexia, and weight decrease) (see **Table 54**).

Table 54. Common Adverse Events ($\geq 5\%$ of Patients) during Treatment and during 24 Weeks Follow-up

Adverse Event	24 Weeks	24 Weeks	48 Weeks	48 Weeks
	PEG-IFN Ribavirin 800 mg No. (%)	PEG-IFN Ribavirin 1000/1200 mg No. (%)	PEG-IFN Ribavirin 800 mg No. (%)	PEG-IFN Ribavirin 1000/1200 mg No. (%)
Headache	102 (49)	136 (49)	187 (52)	239 (55)
Fatigue	98 (47)	135 (48)	182 (50)	211 (48)
Myalgia	91 (44)	120 (43)	154 (43)	163 (37)
Pyrexia	81 (39)	114 (41)	156 (43)	173 (40)
Insomnia	69 (33)	99 (35)	146 (40)	146 (33)
Nausea	64 (31)	91 (33)	107 (30)	151 (35)
Rigors	64 (31)	87 (31)	87 (24)	119 (27)
Irritability	59 (29)	76 (27)	96 (27)	112 (26)
Arthralgia	50 (24)	70 (25)	106 (29)	105 (24)
Alopecia	53 (26)	74 (26)	106 (29)	92 (21)
Pruritus	56 (27)	60 (21)	81 (22)	111 (25)
Depression	43 (21)	42 (15)	79 (22)	104 (24)
Diarrhoea	44 (21)	46 (16)	65 (18)	96 (22)
Dermatitis	34 (16)	49 (18)	69 (19)	86 (20)

Appetite decreased	30 (14)	41 (15)	66 (18)	91 (21)
Cough	26 (13)	39 (14)	65 (18)	84 (19)
Asthenia	39 (19)	37 (13)	56 (16)	73 (17)
Dizziness	34 (16)	40 (14)	53 (15)	72 (17)
Dry skin	26 (13)	35 (13)	49 (14)	75 (17)
Injection site Inflammation	22 (11)	39 (14)	57 (16)	58 (13)
Dyspnea	28 (14)	32 (11)	42 (12)	66 (15)
Back pain	19 (9)	38 (14)	50 (14)	44 (10)
Abdominal pain upper	14 (7)	25 (9)	36 (10)	55 (13)
Vomiting	18 (9)	23 (8)	44 (12)	43 (10)
Concentration impairment	16 (8)	31 (11)	35 (10)	44 (10)
Anxiety	21 (10)	23 (8)	28 (8)	40 (9)
Anorexia	13 (6)	20 (7)	29 (8)	46 (11)
Sore throat	17 (8)	19 (7)	29 (8)	40 (9)
Dry mouth	18 (9)	18 (6)	29 (8)	33 (8)
Abdominal pain	14 (7)	15 (5)	27 (7)	38 (9)
Pain	14 (7)	16 (6)	29 (8)	32 (7)
Dyspepsia	9 (4)	18 (6)	20 (6)	40 (9)
Inject site reaction	20 (10)	11 (4)	24 (7)	18 (4)
Dyspnoea exertional	9 (4)	16 (6)	25 (7)	22 (5)
Sinusitis	6 (3)	14 (5)	22 (6)	28 (6)
Epistaxis	8 (4)	16 (6)	18 (5)	26 (6)
Weight decrease	4 (2)	19 (7)	21 (6)	24 (6)
Nasopharyngitis	11(5)	13 (5)	21 (6)	22 (5)
Mouth ulceration	9 (4)	11 (4)	19 (5)	25 (6)
Emotional instab.	11(5)	12 (4)	16 (4)	23 (5)
Malaise	5 (2)	12 (4)	21 (6)	24 (6)
Constipation	11(5)	13 (5)	21 (6)	16 (4)
URI	9 (4)	14 (5)	19 (5)	19 (4)
Taste disturbance	6 (3)	15 (5)	19 (5)	20 (5)
Pain in limb	12(6)	11 (4)	18 (5)	17 (4)
Hypothyroidism	5 (2)	13 (5)	19 (5)	19 (4)
Rash pruritic	9 (4)	7 (3)	14 (4)	25 (6)
Weakness	6 (3)	14 (5)	17 (5)	18 (4)
Sweating increased	5 (2)	13 (5)	14 (4)	20 (5)
Eczema	6 (3)	11 (4)	12 (3)	21 (5)
Herpes simplex	7 (3)	15 (5)	12 (3)	15 (3)
Vision blurred	9 (4)	4 (1)	15 (4)	20 (5)
Mood swings	6 (3)	7 (3)	18 (5)	16 (4)
Muscle cramps	5 (2)	11(4)	17 (5)	13 (3)
Libido decreased	10(5)	6 (2)	17 (5)	10 (2)
Bronchitis	6 (3)	7 (3)	17 (5)	12 (3)
Depressed mood	10(5)	9 (3)	6 (2)	12 (3)

Patient Deaths

Four patients died in this study: one patient in the 24-week standard-ribavirin dose group died after taking an overdose of opiates, one patient in the 48 week low-ribavirin dose group died of septic shock, one patient in 48-week standard-ribavirin dose group committed suicide, while another patient in this group died of multiple drug overdose including amphetamines, opiates, atropines, and alcohol consumed the day before he was found dead (drug toxicity). Three of the four deaths occurred during treatment. The dysphoric effects of interferons may lead to resumption of drug abuse in some individuals making the two deaths due to drug overdose likely attributable to the study treatment.

The septic death was associated with significant neutropenia and was clearly attributable to treatment as was the suicidal death.

Serious Adverse Events

As in the first study, individual serious adverse events were rare (<1%) and were primarily infectious, neuropsychiatric, gastrointestinal, inflammatory and hematologic disorders (**Table 55**). There were more serious adverse events in the 48 week treatment duration arms than in the 24 week duration arm owing to the larger number of participants in those arms as well as the longer exposure to the study medications.

Neuropsychiatric serious adverse events were the most common followed by infections.

Inflammatory/rheumatologic serious adverse events were found in all arms of the study including four cases of newly developing sarcoidosis. Other inflammatory/rheumatologic adverse events included rheumatoid arthritis, systemic lupus erythematosus, and an autoimmune hepatitis. There was one case of uric acid nephropathy with resultant renal insufficiency in the 24 week duration/800mg ribavirin arm.

Table 55. Serious Adverse Reactions by Study Arm and Category

Category of Serious AE	Peg-IFN/Ribavirin 800 mg x 24 weeks N=207		Peg-IFN/Ribavirin 1000-1200mg x 24 weeks N=280		Peg-IFN/Ribavirin 800mg x 48 Weeks N=361		Peg-IFN/Ribavirin 1000-1200mg x 48 weeks N=436	
	N	%	N	%	N	%	N	%
Infections	2	1	3	1	5	1	12	3
Psychiatric	1	<1	6	2	4	1	6	1
Inflammatory/Autoimm	3	1	2	1	5	1	3	1
Gastrointestinal	1	<1	2	1	4	1	4	1
Neurologic			1	<1	5	1	7	2
Metabolic	1	<1	2	1			2	<1
Ophthalmologic					1	<1	1	<1
Dermatologic			2	1	1	<1	1	<1
Trauma					3	1	5	1
Cardiology/Pulm					1	<1	4	1
Vascular			1	<1	1	<1	1	<1
Neutropenia					1	<1		
Neoplasms					1	<1	1	<1
Anemia					1	<1	2	<1
General/Renal	1	<1			2	<1	3	1
Totals	8	4	19	7	37	10	48	11

Serious Infections

Serious infections were the most prevalent of the serious adverse events in this study. As was true for serious adverse events in general, there were more serious infections in the 48 week duration arms than in the 24 week duration arms. Among the two 48 week duration arms, there were twice as many serious infections in the high ribavirin dose compared to the low ribavirin dose (**Table 55**). As in the first study, bacterial causes, either proven or empirically treated, predominated in all 4 study arms. Of the bacteria that were recovered, all would be considered likely members of the patient’s normal resident bacterial flora.

Grade 4 neutropenia was recorded only once among these 22 serious infections, and that was in the case of the individual who died of overwhelming *Staphylococcus aureus* septicemia. That patient was in the 48 week, 800mg ribavirin arm and he sustained a splinter in his hand on day 55 of study treatment. He sought medical attention on day 57, the splinter was removed and his ANC was recorded as being 800. He returned for follow-up at day 60 and antibiotics were recommended but refused. On day 62 he developed high fever, chills and agitation. On day 63 he became oligouric. On day 64 he was transferred from a local clinic to his local hospital with symptoms of severe sepsis. His ANC upon admission to the hospital was initially $2.6 \times 10^9/L$ but 10 hours later it was recorded as 0 and the patient expired of his overwhelming sepsis.

As occurred in the first study, there were frequently significant time intervals between the patient’s last CBC prior to onset of infection and the first recorded CBC after onset (see **Table 56**). As was also seen in the earlier study, there appears to be a blunting of the expected neutrophil response to serious infections as is seen with the case of pyelonephritis in the 24 week, high dose ribavirin arm or the endocarditis in the 48 week, low dose ribavirin group. About half (10/22) of these serious infections had associated significant or severe lymphopenia. As in the first study the significance of this finding is unknown since the overwhelming majority of the infections were suspected or proven to be caused by bacteria.

Table 56. Serious Infections and Corresponding Neutrophil and Lymphocyte Counts

Diagnosis	Onset Day	Resolved Day	Last CBC Prior/day	First CBC After/day	PMN * Nadir	Lymphs* Nadir
Peg-IFN 180µg/Ribavirin 800mg x 24 weeks						
Cystitis(antibiotics given)	16	20	15	29*	$1.1 \times 10^{3*}$	$2.6 \times 10^{3*}$
Pyrexia(indeterinant)	285	288	247	289*	$3.3 \times 10^{3*}$	$2.8 \times 10^{3*}$
Peg-IFN 180µg/ribavirin 1000-1200mgX 24 weeks						
Pyelonephritis	107	113	84	124*	$.99 \times 10^{3*}$	$1.3 \times 10^{3*}$
URTI(bacterial)	217	316	202	251*	$2.4 \times 10^{3*}$	$1.6 \times 10^{3*}$
LRTI(H. influenzae)	127	207	85	127*	$4.9 \times 10^{3*}$	$0.6 \times 10^{3*}$
Peg-IFN 180µg/800mg x 48weeks						
Pneumonia (bacterial)	210	263	169	210*	$2.6 \times 10^{3*}$	$0.4 \times 10^{3*}$
Pneumonia(S. pneumoniae)	353	367	337	365*	$1.9 \times 10^{3*}$	$0.96 \times 10^{3*}$
Peri-anal abscess(E.coli)	57	200	57	85*	$2.3 \times 10^{3*}$	$1.6 \times 10^{3*}$
Septicemia(Staph aureus)	62	65	57	64*	$0.0 \times 10^{3*}$	$1.1 \times 10^{3*}$
Endocarditis(Strep sanguis)	148	174	127	161*	$0.9 \times 10^{3*}$	$0.7 \times 10^{3*}$

Peg-IFN 180µg/Ribavirin 1000-1200mg x 48 weeks						
Pyrexia	139	218	125	163*	1.1x10 ³	1.1x10 ³
Perianal abscess(antibiotic given)	237	295	211	253*	2.3x10 ³	1.5x10 ³
Post op wound infection(staph)	190	228	185	190*	9.8x10 ³	0.4x10 ³
Osteomyelitis(Staph aureus)	118	152	85	125*	2.2x10 ³	1.6x10 ³
Pyelonephritis(E. coli)	47	51	44	89*	1.2x10 ³	0.6x10 ³
Leg ulcer cellulitis(antibiotics)	19	111	15	29*	1.3x10 ³	0.7x10 ³
Pyelonephritis(E. coli)	37	44	29	47*	1.5x10 ³	1.1x10 ³
Pyelonephritis(E. coli)	70	86	58	86*	1.2x10 ³	0.8x10 ³
UTI (E.Coli)	204	225	169	207*	2.9x10 ³	0.7x10 ³
Amoebiasis(antibiotics given)	93	115	85	127*	1.0x10 ³	0.9x10 ³
Spontaneous B peritonitis(antibiot)	188	196	183*	203	1.3x10 ³	0.4x10 ³
Peri-Tonsilar abscess(antibiotics)	323	327	295	337*	1.7x10 ³	1.2x10 ³

Withdrawal from Treatment because of Adverse Events or Laboratory Abnormalities

The percentages of patients withdrawing from treatment due to an adverse event or laboratory abnormality were higher among patients treated for 48 weeks (15-16%) than among patients treated for only 24 weeks (5%) (see **Table 57**). Adverse events accounted for 80% of withdrawals in this group. Neuropsychiatric disorders including depression, suicide attempt, and anxiety were the most frequent adverse events leading to withdrawal and were proportionally higher in the 48 week arms than in the 24 week (4% versus 1.6%). Depression was the most common single cause in both the 24 and 48 week duration groups.

The second most common adverse events leading to withdrawal were general disorders such as fatigue, pyrexia and asthenia which resulted in 2.1% of the withdrawals in the 48 week group and 0.4% of the 24 week. The next most common group of adverse events that lead to withdrawal was rashes, dermatitis, alopecia. Rarer causes ($\leq 1\%$) included sarcoidosis, abdominal pain, autoimmune thyroiditis, myalgias/artralgias, worsening of underlying diabetes, systemic lupus erythematosus. Laboratory abnormalities were uncommon causes for withdrawal (approx 20%). Of these, neutropenia was the most frequent with 11 withdrawals, followed by worsening liver associated enzymes and thyroid abnormalities both hyperthyroidism and hypothyroidism.

Table 57. Withdrawals for Laboratory Abnormalities/ Adverse Events

<u>WD-Reason</u>	PEG-IFN/Ribavirin 800 mg x 24 weeks N=207	PEG-IFN/Ribavirin 1000-1200mg x 24 weeks N=280	PEG-IFN/Ribavirin 800mg x 48 Weeks N=361	PEG-IFN/Ribavirin 1000-1200mg x 48 weeks N=436
Patient numbers	10(5%)	13(5%)	59(16%)	67(15%)
LAB ABNORMAL	2	3	9	16
Neutropenia	1	1	5	4
Thrombocytopenia	1		1	1
Anemia				2
Liver Assoc Abn		2	1	5
Thyroid Abnorm			2	4
ADVERSE EVENTS	8	10	50	51
General	1	1	11	11
Psychiatric	6	3	12	18

Infections		1	4	1
GI/ABD Pain		1	1	2
Endocrine			2	2
DERM/Alopecia	1	2	6	5
Neurologic			3	2
Rheum/inflamm			5	4
Ophthalmologic			1	
Trauma				1
Hypersensitivity				1
Pulm/Card/CP			1	4
DVT			1	
Cancer			1	
Sarcoidosis			1	
Other			1	
TOTAL	10	13	59	67

Dose Modifications for Adverse Events or Laboratory Abnormalities

Peg-IFN

Laboratory abnormalities were more frequent than adverse events as the reason for dose modification. Approximately 20% of patients in all four study arms required modification of their PEG-IFN because of neutropenia, and 4% for thrombocytopenia. The percentages were slightly higher in the 48 week therapy duration groups and the 24% observed in the high ribavirin arm agrees well with the 24-25% values in the same arm in the first study.

Ribavirin

Adverse events were more common than laboratory abnormalities as a cause for modification of the ribavirin dose. Anemia was by far the most common laboratory abnormality leading to dose modification and was more frequent in the higher dosage, longer duration. The difference in the incidence of dose modifications for anemia between patients receiving 1000 or 1200 mg of ribavirin and patients receiving 800 mg of ribavirin was more pronounced in the group of patients randomized to 48 weeks of treatment (19% v.s. 9%) than among patients randomized to 24 weeks of treatment (11% vs 8%) (see **Table 58**).

Table 58. Adverse Events and Laboratory Abnormalities Leading to Dose Modification

	Peg-IFN α2a	Ribavirin Low x 24 weeks	Peg-IFN α2a	Ribavirin High x 24 weeks	Peg-IFN α 2a	Ribavirin Low x 48 weeks	Peg-IFN α2a	Ribavirin High x 48 weeks
AE or Lab abnormality	63(30)	39(19)	73(26)	76(27)	120(33)	101(28)	159(36)	166(38)
AE	15(7)	24(12)	25 (9)	50(18)	41(11)	70(19)	60(14)	98(22)
Lab abnormality	4 (23)	17(8)	55(20)	33(12)	90 (25)	37(10)	121(28)	89(20)
ALT			2 (<1)		1(<1)		6(1)	
Anemia		16(8)	1(<1)	31(11)	1(<1)	33(9)	1(<1)	85(19)
Neutropenia	42(20)	1(<1)	46(16)	1(<1)	79(22)	2(<1)	106(24)	3(<1)

Thrombocytopenia	9(4)	1(<1)	10(4)		14(4)	2(<1)	20(5)	2(<1)
Other Lab abnorm	1(<1)			1(<1)		2(<1)		

Laboratory Data: Neutropenia

In all four treatment groups median neutrophil counts decreased to a similar degree, with the largest decreases occurring during the first 4 weeks of treatment. Median neutrophil counts then stabilized and remained at around 40% of their baseline value until the end of treatment. Neutrophil counts increased following the end of treatment, returning to normal values within roughly 4 weeks after the end of treatment (see **Figures below**)

Median Neutrophil Counts during Treatment and 24 Weeks Posttreatment



A summary of patients' lowest neutrophil counts during the study is shown in **Table 59**. There was no difference in the incidence of grade 4 neutropenia between patients assigned to 48 weeks and patients assigned to 24 weeks of treatment (both groups approximately 5%). The percentage of patients experiencing grade 3 neutropenia, however, was lower in the 24 week than in the 48 week treatment groups (51% vs 41%). The incidence of grade 3 and 4 neutropenia in the PEG-IFN containing arms of the previous study is similar.

Table 59. Summary of Patients' Lowest Neutrophil Counts during Treatment and 24 Weeks Post-treatment

	Normal >2	Grade 1 1.5-1.99	Grade 2 1.0-1.49	Grade 3 0.5-0.99	Grade 4 <.5
Peg-IFN/Ribavirin 800 mg x 24 weeks N=207	12(6)	27(13)	71(34)	87(42)	10(5)
Peg-IFN/Ribavirin 1000-1200mg x 24 weeks N=280	18(6)	36(13)	102(36)	115(41)	8(3)

Peg-IFN/Ribavirin 800mg X48 weeks N=361	14(4)	36(10)	122(34)	172(48)	17(5)
Peg-IFN/Ribavirin 1000-1200mg x48 weeks N=436	19(4)	27(6)	137(31)	232(53)	20(5)

Laboratory Data: Thrombocytopenia

Median platelet counts decreased from baseline during the first 8 weeks of treatment in all four groups and remained stable until the end of treatment. In all groups, median platelet counts increased to almost baseline levels within 4 weeks after the end of treatment (week 28 or week 52, respectively).

Patients treated for 24 weeks

Patients treated for 48 weeks

The decrease in median platelet counts was slightly less in patients receiving a higher dose of ribavirin, the difference being more noticeable in the group of patients treated for 24 weeks. None of the patients had their platelet counts decrease to below 20×10^9 cells/L (grade 4 thrombocytopenia), and the incidence of grade 3 thrombocytopenia was low ($\leq 5\%$), with no apparent differences between treatment groups. The proportions of patients experiencing grades 1 and 2 thrombocytopenia were also similar in all treatment groups. Thrombocytopenia was not associated with serious bleeding events, as only four serious bleeding events occurred during the study and none of these were preceded by platelet counts below 50×10^9 cells/L (see **Table 60**).

Table 60. Number of Patients with Thrombocytopenia during Treatment and 24 Weeks Post-treatment

	Normal ≥ 100	Grade 1 75-<100	Grade 2 50-75	Grade 3 20-50	Grade 4 <20
Peg-IFN/Ribavirin 800 mg x 24 weeks N=207	143 (69)	41(20)	15(7)	8(4)	0(0)
Peg-IFN/Ribavirin 1000-1200mg x 24 weeks N=280	199 (71)	44(16)	2 (10)	9(3)	0(0)
Peg-IFN/Ribavirin 800mg x48 weeks N=361	250(69)	70(19)	26(7)	15(4)	0(0)

Peg-IFN/Ribavirin 1000-1200mg x48 weeks N=436	274(63)	87(20)	53(12)	21(5)	0(0)
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Laboratory Data: Anemia

Median hemoglobin concentrations declined during the first 8 weeks of treatment, then stabilized and returned to baseline levels within 12 weeks after the end of treatment.

Patients receiving higher doses and/or longer exposure to ribavirin were more likely to experience falls in hemoglobin to <10 g/dl (**Table 61**). A total of 11 patients had their hemoglobin concentration decrease to below 8.5 g/dL. Hemoglobin levels did not decrease to <8.5 g/dl in any patient in the group treated for 24 weeks with 800 mg of ribavirin.

Table 61. Lowest Hemoglobin Levels During Treatment and Post-Treatment

	8.5-<10g/dl	<8.5g/dl
Peg-IFN/Ribavirin 800 mg x 24 weeks N=207	7(3)	0(0)
Peg-IFN/Ribavirin 1000-1200mg x 24 weeks N=280	24(9)	4(1)
Peg-IFN/Ribavirin 800mg X48 weeks N=361	22(6)	1(<1)
Peg-IFN/Ribavirin 1000-1200mg x48 weeks N=436	61(14)	6(1)

Exploratory Analysis: The effect of BMI upon Occurrence of Hematologic Toxicity

In this second study, the differences between the two BMI groups is most noticeable in the higher percentage of significant anemia in the two high ribavirin dose arms (8-10% higher). The incidence of Grade 3/4 neutropenia was consistently higher in the BMI <25 group in all 4 study arms although again, there was less difference when Grade 4 Neutropenia is separately considered. As in the first study, Grade 3/4 thrombocytopenia paradoxically appeared to have higher incidence in the BMI ≥25 group in all arms except for the 24 week, high dose ribavirin (see **Table 62**).

Table 62. Occurrence of Hemoglobin <10, Grade 4 Neutropenia, Grade 3/4 Neutropenia, and Grade 3/4 Thrombocytopenia in Patients Categorized by BMI

	PEG-IFN/Ribavirin 800 mg x 24 weeks N=207		PEG-IFN/Ribavirin 1000-1200mg x 24 weeks N=280		PEG-IFN/Ribavirin 800mg x 48 weeks N=361		PEG-IFN/Ribavirin 1000-1200mg x 48 weeks N=436	
	BMI < 25 N=93 %	BMI ≥ 25 N=114 %	BMI < 25 N=123 %	BMI ≥ 25 N=157 %	BMI < 25 N=170 %	BMI ≥ 25 N=191 %	BMI < 25 N=190 %	BMI ≥ 25 N=246 %
Hemoglobin <10 g/dl	4	3	16	6	7	6	20	12
Grade 3/4 Neutropenia	57	39	47	41	56	49	62	54
Grade 4 Neutropenia	7	4	4	2	6	4	4	5
Grade3/4Thrombocytopenia	1	6	5	2	3	5	3	6

Triglyceride levels

Triglyceride levels were elevated (up to several fold) in a number of patients during the treatment period.

CONCLUSIONS

Efficacy

In patients infected with HCV genotype 1, peginterferon alfa2a –based therapy (180 ig sc once weekly) in combination with standard ribavirin dose (1000 mg for BW < 75 kg or 1200 mg for BW >75 kg po daily) administered for 48 weeks induces a higher proportion of sustained virologic response when compared to:

- shorter duration of therapy (24 weeks) in combination with standard (1000/1200 mg) or low (800 mg) ribavirin dose
- similar duration of therapy (48 weeks) in combination with low (800 mg) ribavirin dose

In patients infected with HCV genotype Non-1, peginterferon alfa-2a (180 ig sc once weekly) in combination with low ribavirin dose (800 mg po daily) for 24 weeks induces sustained virologic response rates that appear to be similar to those induced by:

- standard ribavirin dose (1000 or 1200 mg po daily based on body weight)
- longer duration of therapy (48 weeks) in combination with either low or standard ribavirin dose

There are few data in patients infected with the following “subsets” of HCV genotype non-1: genotypes 4, 5, and 6. Therefore firm recommendations about the optimal treatment regimen for these patients cannot be made. Nevertheless in the 36 patients infected with genotype 4 there was a suggestion that response was dependent on ribavirin exposure with highest response in the 48-week, standard-ribavirin dose regimen.

End-of-treatment virologic response was a secondary efficacy outcome, whereas 24 week post-treatment (sustained) response was the primary efficacy outcome. The end-of treatment virologic response in patients treated for 24 weeks appears to be higher than the end-of treatment virologic response for patients treated for 48 weeks irrespective of HCV genotype. This observation is not consistent with the primary efficacy outcome.

This study confirmed the association between lower response to treatment and the following factors: HCV genotype and titer, cirrhosis, older age, increased body weight, African-American origin, US participants.

Safety

Duration of peginterferon alfa-2a and ribavirin combination treatment for 24 weeks was associated with lower incidence of severe or serious adverse events, lower withdrawal rates, and lower need for modification of interferon and ribavirin dose when compared to 48 weeks of therapy. Low (800 mg) ribavirin dosage was also associated with lower need for ribavirin dose modification and slightly lower serious adverse events compared to standard (1000 or 1200 mg) ribavirin doses.

Serious infections in particular were more numerous in the 48 week/standard-ribavirin. Withdrawals for neutropenia were also highest in this group and there was an association between neutropenia and a fatal outcome from bacterial sepsis.

Risk benefit

It appears that in patients with genotype non-1, 24 weeks of therapy with peginterferon alfa-2a (180 ig) in combination with low ribavirin dose (800mg) is associated with less serious toxicity when compared to 48 weeks of peginterferon alfa-2a therapy with low or standard ribavirin dose. This regimen does not appear to be associated with reduced treatment response.

APPENDIX 1

Subgroup Analysis. Virologic Response by Body Weight and Geographic Region

Overall, the greater the patient’s baseline weight, the lower the proportion of virologic response for all three treatment groups (Table 17). The numbers of participants in the higher weight groups is considerably greater in the US. The US had 64% of the participants >85kg in the monotherapy arm, 60% of the Peg-IFN/ribavirin arm participants >85kg and 67% of the IFN/ribavirin arm participants >85kg.

Table 17. Virologic Response^a by Body Weight and by Geographic Region

	PEG-IFN alfa 2a			PEGIFN alfa 2a ribavirin			IFN alfa 2b ribavirin		
	Total N-SVR	US N-SVR	Non US N-SVR	Total N-SVR	US N-SVR	Non US N-SVR	Total N-SVR	US N-SVR	Non US N-SVR
All BW	224(29)	93(26)	131(31)	453(53)	184(42)	269(61)	444(44)	183(36)	261(50)
BW <64	35(40)		35(40)	59(66)	0	59(66)	81(51)	0	81(51)
<74	71(27)	27(37)	44(20)	128(62)	40(70)	88(58)	117(42)	45(40)	72(43)
75-<85	46(33)	20(25)	26(38)	117(48)	54(35)	63(59)	111(49)	47(34)	64(59)
85-98	51(25)	25(20)	26(31)	104(49)	45(33)	59(61)	85(44)	41(39)	44(48)
>98	21(19)	21(19)		45(36)	45(36)		50(32)	50(32)	

^aSustained virologic response

Subgroup Analysis: Virologic Response by Genotype, Viral Load and by Geographic Region

Of all the factors influencing a HCV-infected patient’s response to treatment, the most important appears to be genotype. Genotype 1 is the most difficult to treat, especially for subjects who also have a high viral titer which is defined for this study as a circulating HCV titer of $>2 \times 10^6$ ~~virions~~ copies/ml of serum. In this study, response rates for genotype 1 were substantially lower than those for genotype non-1 in all three arms. In the genotype 1 subgroup PEG-IFN and ribavirin was superior to IFN and ribavirin (44% vs. 36%); however, when analyzed according to region, the treatment differential (difference between PEG-IFN + ribavirin vs. IFN + ribavirin) was larger among the non-US patients.

The treatment difference (PEG-IFN + ribavirin - IFN + ribavirin) appeared to be similar in US and non-US patients in the subset defined by high viral load.

Table 18. Virologic Response^a by HCV Genotype, Titer and by Geographic Region

	Peg-IFN alfa 2a			Peg-IFN alfa 2a ribavirin			IFN alfa 2b ribavirin		
	Total N-SVR	US N-SVR	Non US N-SVR	Total N-SVR	US N-SVR	Non US N-SVR	Total N-SVR	US N-SVR	Non US N-SVR
All Subj.	224(29)	93(26)	131(31)	453/53	184(42)	269(61)	444(44)	183(36)	261(50)
Genotyp1	145(20)	66(11)	79(28)	298(44)	128(31)	170(54)	285(36)	128(29)	157(42)
Non-1	79(46)	27(63)	52(37)	155(70)	56(68)	99(72)	159(60)	55(53)	104(63)
Titer:low	69(45)	27(26)	42(57)	159(57)	64(41)	95(68)	150(53)	56(45)	94(57)
high	155(22)	66(26)	89(19)	293(51)	119(44)	174(56)	292(40)	125(33)	167(46)

^aSustained virologic response

A logistic regression analysis including genotype, viral titer, geographic region, and weight found that the geographic region was not a significant factor contributing to treatment response. Thus, the differences in sustained virological response for the overall population observed between US and non-US patients appear to be largely due to imbalance in other important prognostic factors for response.