

sion in R. M. (Table 2) in 1979, while conventional readings of serial biopsies were unchanged. A liver biopsy performed at another hospital approximately 1 year later was interpreted conventionally as showing deterioration from the 1979 biopsy (Dr. Matthew Janin, personal communication). It does appear that changes in liver histology are an appropriate "gold standard" by which disease activity can be measured in patients with asymptomatic CAH. The HAI system outlined allows for easy, objective, and reproducible quantitation of histological change in serial liver biopsy specimens from patients with asymptomatic CAH. It provides data which are readily amendable to statistical analysis. While conventional readings of biopsies can also be available for evaluation, employment of a system to score numerically liver biopsies appears to be a concept worthy of consideration in following and studying patients with asymptomatic CAH.

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APPENDIX B

**MEDICAL OFFICER'S REVIEW OF NDA 20-903
STUDY I95-145**

DRAFT

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1. PROTOCOL SUMMARY

1.1. Study Title

"Interferon Alpha-2b (Intron® A) Monotherapy versus Interferon Alpha-2b (Intron A) + Ribavirin (Rebetol™) for Treatment of Relapse in Patients with Chronic Hepatitis C"

1.2. Objective

The objective of this study was to compare the safety and efficacy of ribavirin + interferon alpha-2b (IFN) combination therapy to placebo + IFN in patients with chronic hepatitis C (CHC) who relapsed after successful interferon monotherapy.

1.3. Study Design

The study was a phase 3, multicenter, randomized, double-blind, parallel group design employing two treatment arms, i.e., ribavirin + IFN compared to placebo + IFN. Enrollment of approximately 150 patients with CHC were projected at 15 international study centers. Patients were randomized to treatment arms in a ratio of 1:1. The duration of this study was 48 weeks, which included a 24-week treatment phase and a 24-week post-treatment follow-up period to determine durability of treatment response.

Patients were stratified with respect to the following characteristics: presence or absence of cirrhosis, hepatitis C virus (HCV) genotype (type 1 or other), and HCV RNA \leq 2,000,000 copies/mL or HCV RNA $>$ 2,000,000 copies/mL.

Serial ALT and HCV RNA levels were performed during treatment and post-treatment follow-up. In addition, blinded histopathological comparisons of pre-treatment and post-treatment (obtained at week 48) liver biopsies were to be conducted by a central pathologist using Knodell Histology Activity Index (HAI) scores. During treatment phase, patients were assessed every 2 weeks for the first 8 weeks, and every 4 weeks thereafter for clinical adverse events and laboratory tests. Similar assessments were to be conducted during post-treatment follow-up at weeks 4, 8, 12 and 24.

Reviewer's Comment

The applicant reported "some" stratification errors during the randomization process, e.g., miscoding of HCV genotype. Information on these errors were not submitted for review. According to the applicant, the errors were corrected prior to final analysis and no biases were introduced by these errors.

1.4. Study Population

The study enrolled patients with CHC, 18 years or older, who had relapsed, as evidenced by abnormal ALT levels, within 1 year after showing initial response to 1 or 2 courses of IFN treatment (3 MU to 6 MU QOD or TID for 20 weeks to 18 months). To be eligible, patients had to have positive serum HCV by PCR assay, documented abnormal ALT levels (within 3 months of entry), and liver biopsy (within 6 months of entry) showing evidence consistent with chronic hepatitis. Other entry criteria included Hb > 12 g/dL and 13 g/dL for females and males, respectively; WBC \geq 3,000/mm³; platelets \geq 100,000/mm³; PT \leq 2 seconds prolonged compared to control; albumin \geq 3.5 g/dL; indirect bilirubin \leq 0.8 mg/dL; direct bilirubin \leq 0.3 mg/dL; creatinine \leq 1.4 mg/dL; fasting blood glucose \leq 115 mg/dL (for non-diabetic patients); HbA_{1c} \leq 8.5% (for diabetic patients); normal TSH level; ANA titer \leq 1:160; normal AFP level, no evidence of hepatocellular carcinoma on ultrasound; negative HBsAg; and negative HIV status. Patients had to practice adequate birth control during the study. History of ribavirin use, active illicit I.V. drug use, pregnancy, breast-feeding, heavy alcohol consumption (> 20 g/day), and participation on other investigational therapy were reasons for exclusion. Patients with pre-existing psychiatric conditions, significant cardiovascular dysfunctions within the previous 6 months (e.g., angina, CHF, recent MI, severe HTN, or significant arrhythmia), coexisting liver disease, and recipients of organ transplantation were not allowed to participate in this study.

Reviewer's Comment

Six patients (3%) had evidence of cirrhosis on pre-treatment liver biopsy. However, it appears that none of these patients had uncompensated cirrhosis (jaundice, ascites, variceal hemorrhage, or encephalopathy). Three of these patients were on the ribavirin + IFN arm, the other 3 on the placebo + IFN arm.

1.5. Patient Treatment

The study regimens were IFN 3 MU SC TIW + ribavirin 600 mg PO BID; or IFN 3 MU SC TIW + placebo in two divided doses for 24 weeks. Patients weighing \leq 75 Kg were to receive 1,000 mg of ribavirin daily (2 capsules in the morning and 3 capsules in the evening).

Reviewer's Comment

The interferon dose was the approved dose for treatment of chronic hepatitis C. The dosages for ribavirin were based on previous studies of ribavirin for chronic hepatitis C.

1.6. Dose Reduction and Treatment Discontinuation

Patients with Hb decrease to < 10 g/dL (or a decrease of 2 g/dL in 4 weeks in patients with pre-existing cardiovascular diseases) while on treatment would have ribavirin/placebo reduced to 600 mg per day for at least 4 weeks. Regular ribavirin dosing would only resume when Hb returned to ≥ 11 g/dL (or ≥ 12 g/dL in those with cardiac conditions). IFN dose was to be decreased to 1.5 MU TIW in patients who experienced WBC < 1,500/mm³, ANC < 750/mm³, or platelets < 50,000/mm³ until the condition resolved or stabilized.

Patients with hemoglobin < 8.5 g/dL (or < 12 g/dL for 4 weeks in patients with cardiovascular diseases), WBC < 1,000/mm³, ANC < 500/mm³, platelets < 25,000/mm³, direct bilirubin > 2.5xULN, indirect bilirubin > 4 mg/dL, AST/ALT $\geq 2X$ baseline and > 10x ULN would be permanently discontinued from the study.

Reasons for treatment discontinuation or dose reduction were graded based on a hierarchy of importance in the following order: suicide ideation, cardiovascular disorders, other psychiatric disorders, CNS disorders, cardiac or valvular disorders, arrhythmias, respiratory disorders, neoplasms, infections, and allergy.

All patients withdrawn from the study would undergo similar clinical and laboratory follow-up protocols as for those who would complete the 24-week study.

Reviewer's Comment

Patients would receive reduction of ribavirin dose when the hemoglobin levels dropped below 10 g/dL. For those who entered the study with normal baseline hemoglobin levels (e.g., Hb of 15.0 g/dL) they would have experienced significant anemia before ribavirin dose modification took place.

1.7. Concomitant Medications

Concomitant medications were recorded at each visit. Patients could take acetaminophen or other nonsteroidal anti-inflammatory agents for "flu-like" symptoms associated with IFN administration.

1.8. Treatment Compliance

Compliance was monitored by counting returned ribavirin capsules and IFN vials, reviewing of patient treatment diary, and questioning patients about medication administration. To be considered compliant, the patient would have to take at least 80% of the protocol doses.

1.9. Endpoints

1.9.1. Safety

Treatment-emergent adverse events (clinical and laboratory) defined as new events or worsening of existing events were monitored throughout the study. The intensity of adverse events were graded using the modified WHO guidelines. The relationship of an adverse event to treatment was rated by the investigator as unrelated, possibly related, probably related, and related to treatment.

Reviewer's Comment

The protocol did not provide specific criteria for assessment of adverse events and their relationship with treatment. The lack of uniform criteria, together with the subjective nature of rating treatment relationship by individual investigators, raises concern about its analytical validity.

1.9.2. Efficacy

The primary endpoint was the overall response rate. Overall response rate was defined as the proportion of patients with sustained virological response who had improvement of liver histology by 2 points or more in Knodell HAI "inflammation" score (defined as the sum of components I, II and III).

The secondary endpoints were: (1) virologic response rate at end of treatment, (2) proportions of patients with normalization of ALT at weeks 24 and 48, (3) proportions of patients with overall improvement of liver biopsy findings (based on inflammation scores), and (4) changes from baseline of liver biopsy Knodell HAI Inflammation" scores.

The amended protocol specified that a patient with HCV RNA < 100 copies/mL at any time point would be classified as "responder" at that time point. A patient with HCV RNA < 100 copies/mL at 24 weeks of follow-up period would be classified as "sustained responder." A patient would be classified as "non-responder" if the above criteria were not met or if the patient discontinued the study before the required HCV RNA measurements were obtained. Similar criteria were applicable to ALT levels.

In the NDA application, the applicant presented the following additional criteria and analyses that were not defined in the original protocol:

1. The applicant defined a scoring system for evaluation of fibrosis (Knodell HAI component IV) in liver biopsy. Improvement, no change, and worsening of fibrosis were defined as component IV score changes of ≤ -1 , 0, and ≥ 1 , respectively.
2. The applicant introduced an additional method to evaluate liver biopsy based on the METAVIR scoring.
3. The applicant defined additional criteria for sustained virological response. To be classified as a "sustained responder," a patient would have to complete at least 141 follow-up days (> 20 weeks), and the HCV RNA levels would have to be less than 100 copies/mL between days 141 (week 20) and 196 (week 24) of the follow-up period. If the patient had no HCV RNA evaluations during that time, the first HCV RNA measurement after day 196 of follow-up would have to be negative.

Reviewer's Comments

1. In evaluating pre-treatment and post-treatment liver biopsy changes, the applicant chose to consider only the "inflammation" score. The "inflammation" score, as defined by the applicant, referred to the sum of Knodell HAI scores for component I (periportal +/- bridging necrosis), II (intra-lobular degeneration and focal necrosis), and III (portal inflammation) score. While the "inflammation" score represents the degrees of necroinflammatory activity, it does not address the extent of fibrosis or development of cirrhosis. Component IV of Knodell HAI provides numerical assessment of fibrosis/cirrhosis. This component is related to the time course of disease and has significant prognostic and therapeutic implications (1). Therefore, the histological changes between pre-treatment and post-treatment biopsies may be best evaluated with all 4 components of the Knodell HAI. The composite score (I+II+III+IV) in this case reflects both severity and progression of disease.

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ON ORIGINAL**

2. *The definition of sustained virological response by the applicant underwent several revisions. The original protocol defined sustained virological response as HCV RNA measurements < 100 copies/mL at the end of treatment (week 24) and at the end of follow-up (week 48). The protocol definition of sustained response was amended while the trial was in progress specifying sustained virological response as HCV RNA < 100 copies/mL "at 24 weeks of follow-up." It was not clear whether "at 24 weeks of follow-up" implied that HCV RNA measurements at weeks 24, 36 and 48 would have to be negative to be considered "sustained" virological response. Subsequently in the NDA submission, the applicant further revised the definition of sustained virological response as HCV RNA measurement(s) < 100 copies/mL when performed between days 141 (week 40) and day 196 (week 48). By this "post hoc" definition, the applicant essentially counted any patient with a single HCV RNA (at week 48) measurement of < 100 copies/mL as having "sustained" virological response, regardless of any previous HCV RNA results.*

3. *To be considered as having "sustained" virological response, a patient's HCV RNA level at the end of treatment (week 24) should be below the limit of quantification (i.e., < 100 copies/mL), and this virological response should be maintained throughout the follow-up period; i.e., HCV RNA measurements at weeks 36 and 48 should also be below limit of quantification.*

4. *Due to its "post hoc" introduction, a critical review of biopsy data using the METAVIR scoring system was not conducted.*

1.9.3. Quality of Life

Health-related quality-of-life questionnaires consisting of 3 domains (disease-specific, generic, and vitality) were completed by patients at entry, weeks 12, 24, 36 and 48 (see Appendix E, NDA 20-903, Protocol No. I95-145, Volume 3.61, page 597).

1.10. Analytical and Statistical Plans

1.10.1. Safety

Adverse events and laboratory abnormalities were summarized by treatment group for all treated patients.

1.10.2. Comparability of Treatment Groups at Baseline

Treatment groups were compared with respect to demographic and disease characteristics at baseline. Chi-square test was used for gender, race, exposure source, genotype, presence of cirrhosis, and Knodell HAI category IV (fibrosis) score. The Wilcoxon rank sum test was used for age, weight, duration of exposure, ALT, AST, and Knodell HAI score of categories I, II, and III.

1.10.3. Efficacy

1.10.3.1. Primary Efficacy Analysis

The applicant compared the overall response rate, based on all treated patients, using a logistic regression model with main effects due to treatment, genotype, presence of cirrhosis, HCV and baseline Knodell HAI score of categories I, II, and III. The main effects were estimated by "maximum likelihood estimate" method (i.e., patients with negative HCV RNA but missing liver biopsy could be included in the analysis). The applicant also performed additional analysis based on patients with both pre-treatment and post-treatment biopsy evaluations using a standard logistic regression procedure.

1.10.3.2. Secondary Efficacy Analysis

For secondary endpoints, Fisher's exact test was used for comparing proportions of patients with normalization of ALT at weeks 24 and 48, proportions of patients with improvement in liver biopsy (categories I, II, and III), and response rate based on HCV RNA at week 24. A t-test was used to compare changes from baseline in the liver biopsy scores (category I, II, and III). Paired t-test was used for comparisons within treatment groups.

In addition, changes from baseline of HCV RNA were descriptively presented by treatment group.

1.10.4. Quality of life

The applicant planned to present mean values of domain scores and changes from baseline scores. The treatment group comparisons for quality of life were performed by analysis of covariance. The correlation between quality of life scores and clinical efficacy variables was assessed based on Spearman's correlation coefficient.

Reviewer's Comment

The quality-of-life analyses were not evaluated in this review. Please see review by DDMAC for further information.

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2. RESULTS

The study was conducted at 31 international centers in Europe, Canada, Australia, and Israel from 4/12/96 to 7/17/97. The study results are presented below.

2.1. Patient Disposition

Out of 195 randomized patients, 2 voluntarily withdrew from the study and 1 did not meet eligibility criteria prior to drug administration. Each treatment arm had 96 patients. The number of patients at each center ranged from 3 to 12, with an average of 6 per center. According to the applicant, 186 (96.9%) patients completed the 24-week treatment phase, and 182 (94.8%) completed the 24-week follow-up phase. Summaries of patient disposition is presented in Table 2.1.

Table 2.1. Summary of Patient Disposition

Patient Disposition	Number of Patients			
	Applicant's Analysis		FDA Analysis	
	Ribavirin + IFN	Placebo + IFN	Ribavirin + IFN	Placebo + IFN
Randomized	98	97	98	97
Treated	96	96	96	96
Premature discontinuation:				
- 24-week treatment phase	4	2	5	2
- 48-week follow-up phase	2	2	2	2

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.60)

Reviewer's Comment

The applicant reported that 4 patients on the ribavirin + IFN arm discontinued study drugs during the treatment phase. FDA review showed 5 patients who discontinued study drugs, 4 due to adverse events and 1 due to noncompliance. However, this difference had little impact on study treatment and final result analyses

2.2. Protocol Violation

Per FDA request, on 1/13/98 the applicant provided tabulated data on a total of 20 cases of protocol violation with respect to entry inclusion/exclusion criteria. These cases are summarized in Table 2.2.

Table 2.2. Summary of Protocol Violations

Reason	Number of Patients	
	Ribavirin + IFN (n=96)	Placebo + IFN (n=96)
Different previous IFN therapeutic regimen	1	1
Improper liver biopsy timing	1	3
Indirect bilirubin > 0.8 mg/dL	5	3
Fasting blood sugar > 115 mg/dL		3
HbA _{1c} ≤ 8.5%		1
ANC ≤ 1,500/mm ³	1	
Normal ALT (at entry)	1	
Abnormal TSH	1	1

(Source: NDA 20-903, General Correspondence dated 1/13/98)

Reviewer's Comment

It appeared that these protocol violations did not seriously compromise patient eligibility and had little impact on study treatment and final result analyses.

2.3. Noncompliance

There were 3 noncompliant patients (i.e., taking less than 80% of study drugs), 1 (# 13-03) on the placebo + IFN arm and 2 (# 22-01, 23-03) on the ribavirin + IFN arm.

2.4. Demographic Data

According to the applicant, patients on the 2 treatment arms shared similar demographic characteristics. The data are summarized in Table 2.4.

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Table 2.4. Summary of Demographic Data

Demographics	Number (%) of Patients	
	Ribavirin + IFN (n=96)	Placebo + IFN (n=96)
Gender:		
- Male	63 (66)	59 (61)
- Female	33 (34)	37 (39)
Race:		
- White	94 (98)	89 (93)
- Asian	2 (2)	3 (3)
- Other	-	4 (4)
Age (years):		
- Mean	42.4	44.6
- Range	26 - 76	23 - 69

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.60)

Reviewer's Comment

The study population was predominantly male and almost exclusively Caucasian. Future studies should include a more heterogeneous population with respect to racial distribution.

2.5. Baseline Disease Characteristics

According to the applicant, more than half of the patients (58% on the placebo + IFN arm, 59% on the ribavirin + IFN arm) acquired hepatitis C infection via parenteral transmission. The remainder had no clearly identifiable risk factors and were classified as "sporadic/other" cases. The mean duration of disease were approximately 14 years. The baseline HCV genotypes, HCV levels, ALT levels, and liver biopsy Knodell HAI scores are summarized in Table 2.5.. The data showed that the majority of patients (80% on the placebo + IFN arm, 82% on the ribavirin + IFN arm) had mild portal fibrosis. According to the applicant, 3 patients on each treatment arm had evidence of cirrhosis on entry.

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Table 2.5. Baseline Disease Characteristics

Baseline Disease Characteristics	Number (%) of Patients	
	Ribavirin + IFN (n=96)	Placebo + IFN (n=96)
HCV Genotype:		
1 (total)	54 (56)	52 (54)
- 1a	10 (10)	10 (11)
- 1b	36 (38)	32 (34)
2 (total)	9 (9)	19 (20)
- 2a	7 (7)	16 (17)
3a	31 (32)	22 (23)
4c/4d	2 (3)	1 (1)
6a	-	1 (1)
Missing genotype data	-	1 (1)
HCV RNA level		
$\leq 2.0 \times 10^6$ copies/mL	36 (37)	29 (30)
$> 2.0 \times 10^6$ copies/mL	60 (63)	67 (70)
Mean	3.4×10^6	4.2×10^6
Range		
ALT (times upper normal limit):		
Median	2.7	2.3
Range		
Mean Knodell HAI score:		
I (periportal necrosis)	2.4	2.4
II (intralobular necrosis)	1.8	1.7
III (periportal inflammation)	2.4	2.7
IV (fibrosis)	1.3	1.4
Total (I+II+III+IV)	7.9	8.1

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3:60)

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Comments

1. *The Knodell HAI composite score (I+II+III+IV) ranges* To obtain the composite score, liver biopsy is evaluated for periportal +/- bridging necrosis (component I), intralobular degeneration and focal necrosis (component II), portal inflammation (component III) and fibrosis (component IV). The composite score weighs heavily on component I (periportal +/- bridging hepatocellular necrosis) with maximum score of 10, whereas the highest scores for other categories are 4, since it appears that activity in this component best correlates with severity of disease. A score of 2 is not given. In grading component I, emphasis is placed on the severity of florid lobular necrosis, therefore, a score of 6 is given to marked piecemeal necrosis plus bridging necrosis and 10 for multilobular necrosis. There are no numerical scores of 7 to 9 given to this component. According to the authors, the composite score can be broken into individual components of necrosis (categories I, II), inflammation (component III), and fibrosis (component IV) for additional evaluation of the disease.

2. *Genotypes 1, 2, and 3 are most commonly observed in patients from Europe and the USA. Subtype 1a is the most prevalent, followed by 1b and 3a. Some studies have shown an association between subtype 1b with severe chronic hepatitis, cirrhosis, and potential for carcinogenesis. HCV genotypes 1a or 1b, HCV RNA level > 1.0 x 10⁶ copies/mL, and cirrhosis are associated with poor treatment response to interferon treatment.*

2.6. Concomitant Therapy

Analysis of the applicant's data showed that the majority of patients (77% on the placebo + IFN arm, 79% on the ribavirin + IFN arm) took analgesics/antipyretics during the study to manage "flu-like" symptoms (e.g., fever, headache and myalgia). The most common medication was paracetamol (64% of patients on the placebo + IFN arm, 71% of those on ribavirin + IFN arm). Approximately 6% of patients on the placebo + IFN arm and 5% on the ribavirin + IFN arm took sedatives/hypnotics primarily for control of insomnia. Four patients (4%) on each arm were placed on antidepressants for treatment-emergent depression.

2.7. Safety Outcomes

2.7.1. Drug Exposure

The majority of patients completed the protocol-specified treatment. Approximately 97% of patients on the placebo arm and 95% of those on the ribavirin + IFN arm completed the 24 weeks of therapy.

2.7.2. Adverse Events

Over the 24-week treatment period, 89 (93%) patients on the placebo + IFN arm and 94 (98%) patients on the ribavirin + IFN arm experienced at least 1 adverse event. The majority of adverse events were mild to moderate in intensity. There were no life-threatening adverse events. A comparative summary of adverse events occurring in 2% or more of patients on both treatment arms is presented in Table 2.7.2. The overall incidences of adverse events were comparable across both treatment arms. The most common adverse events (reported in > 20% of patients) were headache, fever, fatigue, "flu-like" symptoms, asthenia, and myalgia. Neuropsychiatric effects previously reported in interferon trials such as insomnia, irritability, depression, anxiety, emotional lability, and cognitive changes, occurred with approximately equal frequencies in both arms. A significantly higher number of patients on the ribavirin + IFN arm reported dyspnea, dizziness, nausea, and taste perversion. Infections and resistance disorders occurred in approximately equal frequency for both groups.

APPEARS THIS WAY
ON ORIGINAL

Table 2.7.2. Adverse Events $\geq 2\%$ in Patients of Study I95-145

Adverse Event	Number of Patients (%)	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
Body as a whole	83 (86)	82 (85)
Headache	45 (47)	41 (43)
"Flu-like" symptoms	28 (29)	31 (32)
Fever	30 (31)	29 (30)
Fatigue	34 (35)	27 (28)
Asthenia	26 (27)	25 (26)
Anorexia	18 (19)	18 (19)
Rigors	12 (13)	8 (8)
Weight loss	5 (5)	6 (6)
RUQ pain	4 (4)	5 (5)
Chest pain	1 (1)	5 (5)
Malaise	2 (2)	4 (4)
Dry mouth	5 (5)	4 (4)
Increased sweating	3 (3)	2 (2)
Allergy	3 (3)	2 (2)
Migraine headache	2 (2)	2 (2)
Musculoskeletal disorders	44 (46)	45 (47)
Myalgia	29 (30)	23 (24)
Musculoskeletal pain	17 (18)	17 (18)
Arthralgia	14 (15)	17 (18)
Psychiatric disorders	42 (44)	41 (43)
Insomnia	15 (16)	20 (21)
Irritability	8 (8)	10 (10)
Somnolence	6 (6)	9 (9)
Depression	10 (10)	8 (8)
Anxiety	7 (7)	7 (7)
Emotional lability	7 (7)	3 (3)
Impaired concentration	4 (4)	2 (2)
Agitation	4 (4)	1 (1)
Nervousness	7 (7)	1 (1)
Gastrointestinal disorders	53 (55)	35 (36)
Diarrhea	8 (8)	12 (13)
Abdominal pain	12 (13)	10 (10)
Nausea	24 (25)	9 (9)
Dyspepsia	6 (6)	8 (8)
Flatulence	2 (2)	5 (5)
Vomiting	6 (6)	1 (1)
Constipation	5 (5)	1 (1)

(Continuing...)

Table 2.7.2. Adverse Events \geq 2% in Patients of Study I95-145

Adverse Event	Number of Patients (%)	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
Skin disorders	36 (38)	22 (23)
Alopecia	16 (17)	11 (11)
Pruritus	12 (13)	8 (8)
Rash, NOS	6 (6)	4 (4)
Dry skin	4 (4)	3 (3)
Psoriasis	2 (2)	1 (1)
Dermatitis, NOS	3 (3)	1 (1)
Nail disorders	2 (2)	-
Respiratory disorders	34 (35)	19 (20)
Coughing, NOS	10 (10)	10 (10)
Coughing, nonproductive	5 (5)	-
Dyspnea	11 (11)	1 (1)
Pharyngitis	9 (9)	7 (7)
Nasal congestion	3 (3)	3 (3)
URI	1 (1)	3 (3)
Rhinitis	-	3 (3)
Pulmonary infection	1 (1)	2 (2)
Bronchitis	2 (2)	2 (2)
Wheezing	-	2 (2)
Epistaxis	3 (3)	1 (1)
Sinusitis	3 (3)	1 (1)
Resistance disorders	13 (14)	11 (11)
Viral infection	5 (5)	8 (8)
Otitis media	1 (1)	1 (1)
Bacterial infection, NOS	-	1 (1)
HSV	4 (4)	1 (1)
Fungal infection, NOS	3 (3)	-
Nervous system disorders	17 (18)	12 (13)
Dizziness	9 (9)	5 (5)
Abnormal gait	-	2 (2)
Paresthesia	4 (4)	2 (2)
Hyperesthesia	1 (1)	1 (1)
Hyposthenia	-	1 (1)
Hypertonia	-	1 (1)
Tremor	-	1 (1)
Vertigo	7 (7)	1 (1)
Confusion	2 (2)	1 (1)

(Continuing...)

Table 2.7.2. Adverse Events $\geq 2\%$ in Patients of Study I95-145

Adverse Event	Number of Patients (%)	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
Cardiac disorders	2 (2)	6 (6)
Palpitation	-	4 (4)
Extrasystole	-	1 (1)
Tachycardia	2 (2)	-
Ear disorders	3 (3)	6 (6)
Tinnitus	2 (2)	3 (3)
Earache	1 (1)	2 (2)
Endocrine disorders	2 (2)	3 (3)
Hyperthyroidism	-	2 (2)
Hypothyroidism	2 (2)	2 (2)
Injection site disorders	6 (6)	7 (7)
Inflammation	5 (5)	4 (4)
Reaction	-	3 (3)
Urinary disorders	7 (7)	6 (6)
Micturition/frequency	1 (1)	4 (4)
UTI	6 (6)	3 (3)
Nocturia	2 (2)	-
Injury	-	2 (2)
Accident	-	2 (2)
Others		
Thirst	-	4 (4)
Prostatic disorder (NOS)	-	2 (2)
Taste perversion	9 (9)	2 (2)
Gingivitis	1 (1)	2 (2)
Stomatitis, NOS	5 (5)	-
Eye pain	3 (3)	1 (1)
Conjunctivitis	3 (3)	-
Tooth disorder	2 (2)	1 (1)
Toothache	2 (2)	-
Decreased libido	2 (2)	1 (1)
Hepatomegaly	2 (2)	-

¹ No life-threatening event reported

NOS: Not Otherwise Specified.

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.60)

Reviewer's Comment

It should be emphasized that this study enrolled patients who had previous exposure to interferon therapy. Therefore, the frequency of adverse events could be expected to be higher in treatment-naive patients.

2.7.2.1. Clinically Important Adverse Events

2.7.2.1.1. Psychiatric Adverse Events

Insomnia, irritability, and depression were the most common psychiatric events in this study. These psychiatric disorders have been previously reported in patients undergoing interferon monotherapy. Their distributions were approximately the same in both treatment arms (see Table 2.7.2.C). Most of these cases were mild in intensity, although 4 patients in the ribavirin + IFN required IFN dose modifications. Two patients, one with persistent insomnia and one with depression and suicidal ideation (both on placebo + IFN arm), were discontinued from the study. There was one suicide by a patient who developed depression while on treatment (see section 2.7.3).

Reviewer's Comments

- 1. The applicant reported 8 cases (8%) of treatment-emergent depression among patients on the ribavirin + IFN arm. FDA review of applicant's data showed a total of 11 cases of depression (11%), 9 cases developed during treatment period (patients # 02-02, 09-05, 13-07, 14-01, 20-05, 21-06, 25-03, 27-02, 34-03), 1 case (patient # 22-07) during follow-up period, and one patient with pre-existing depression prior to enrollment (patient # 22-04).*
- 2. The applicant reported 10 cases (10%) of treatment-emergent depression in the placebo + IFN arm. FDA review showed a total of 11 cases (11%), 9 cases of depression emerging during treatment period (patients # 07-02, 09-02, 14-04, 18-01, 18-10, 19-02, 20-06, 31-02, and 32-03), 1 case of depression during follow-up period (patient # 20-01), and 1 case in which the patient had mild depression prior to entry (patient # 22-06).*
- 3. Overall, treatment-emergent depression occurred in approximately 11% of all patients in this study. Ribavirin did not appear to increase the incidence rate of depression. It is of note that the number of patients with depression was relatively low in this study population. The frequency of treatment-emergent depression in study C95-144 (conducted at U.S. sites) was approximately 20%. Historically, depression was reported in 19% of patients with chronic hepatitis C undergoing Intron® A monotherapy.*

2.7.2.1.2. Dyspnea

A disproportionately high number of patients (11) on the ribavirin + IFN arm experienced dyspnea, i.e., 11 patients versus 1 patient on the placebo + IFN arm. Most of these patients experienced mild symptoms at the time of concurrent anemia. Dyspnea appeared to resolve when hemoglobin levels returned to normal. The applicant observed that the severity of dyspnea was related to individual tolerance rather than the magnitude of anemia.

Reviewer's Comment

It was not clear how the applicant attributed dyspnea to "individual tolerance." In this reviewer's opinion, the disproportionately high cases of dyspnea in the ribavirin + IFN group were most likely secondary to, or exacerbated by ribavirin-induced hemolytic anemia.

2.7.2.1.3. Chest pain

A higher proportion of patients on the placebo + IFN arm reported chest pain (5%) than the ribavirin + IFN arm (1%). The cause of chest pain in patient # 27-01, a 76-year-old woman on ribavirin + IFN arm was linked to anemia. The patient's baseline hemoglobin was 12.1 g/dL and decreased to a nadir of 9.5 g/dL. Two cases of chest pain among patients on the placebo + IFN arm were attributable to preexisting bundle branch block and supraventricular beats. The etiology of chest pain for the remaining cases were unclear.

Reviewer's Comments

1. FDA's data analysis confirmed the applicant's impression that the episode of chest pain experienced by patient # 27-01 above was temporally related to her hemoglobinemia. The patient also experienced dyspnea, and a new onset of heart murmur was noted at that time. She was discontinued from therapy. Her symptoms subsequently resolved.

2. Patients with preexisting cardiovascular disorders were excluded from this study. Therefore, the true incidence of exacerbated coronary heart disease due to ribavirin-induced anemia was not known.

2.7.2.2. Serious and Life-threatening Adverse Events

A total of 13 patients (6 in the placebo + IFN group (6%) and 7 in the ribavirin + IFN group (7%)) experienced serious adverse events during the entire study period. There was one treatment-related death by suicide (see discussion in section 2.7.3). These cases are summarized in Table 2.7.2.2.

Table 2.7.2.2. Summary of Serious Adverse Events

Patient ID	Adverse Event	Outcome
Ribavirin + IFN		
09-01	Cholelithiasis	Completed study
11-06	Gluteal abscess	Completed study
20-04	Drug overdose	Completed study ³
22-07	Abdominal pain after liver biopsy	Completed study
27-01	Abnormal ECG	Completed study
33-01	Arterial thrombosis	Lost to follow-up
33-03	Carpal tunnel syndrome	Completed study
Placebo + IFN		
13-08	Bundle branch block	Completed study
19-02	Hyperthyroidism	Completed study
20-01	Hyperthyroidism	Completed study
20-06	Death from suicide	Discontinued ¹
22-02	Suicide ideation	Discontinued ²
31-01	Hemorrhoids	Completed study

¹ See section 2.7.3

² See section 2.7.1.1

³ See section 2.7.10

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.60)

Reviewer's Comment

Some of the serious adverse events listed above were probably related to treatment as discussed elsewhere in this review.

2.7.2.3. Adverse Events Associated with Premature Discontinuation of Treatment

A total of 6 patients, 2 (2%) on the placebo + IFN arm and 4 (4%) on the ribavirin + IFN arm, experienced adverse events that resulted in premature discontinuation of treatment. The adverse events were related to interferon treatment in 4 patients and ribavirin in the other 2. These cases are summarized below:

Case 1. Patients # 02-02 (ribavirin + IFN arm), a 60-year-old woman, developed moderate anorexia and asthenia at the onset of study and mild depression on day 16 thought to be possibly related to treatment. This patient elected to stop treatment on day 21.

Case 2. Patient # 08-07 (placebo + IFN arm), a 42-year-old woman, was discontinued from the study on day 127 due to moderate insomnia and irritability thought to be possibly related to treatment.

Case 3. Patient # 21-06 (ribavirin + IFN arm), a 43-year-old man, developed mild depression, mood changes, and lightheadedness at the beginning of the study. He elected to stop treatment on day 7.

Case 4. Patient # 22-02 (placebo + IFN arm), a 31-year-old man, developed severe suicidal ideation approximately 85 days into the study. The patient elected to stop treatment on or about day 116.

Case 5. Patient # 11-05 (ribavirin + IFN arm), a 37-year-old man, experienced severe shortness of breath and persistent nonproductive cough on day 43 thought to be probably related to treatment. According to the applicant, the patient stopped treatment on day 57 due to "dry cough." A hemoglobin drop of 2.3 g/dL was incidentally also noted at the time of this event.

Case 6. Patient # 27-01 (ribavirin + IFN arm), a 76-year-old woman, experienced chest pain and dyspnea when her hemoglobin dropped from 12.5 g/dL at baseline to 9.5 g/dL on day 133. She was discontinued from treatment on day 167.

Reviewer's Comments

1. While dry cough has been previously reported in patients undergoing interferon monotherapy, severe dyspnea reported by the patient in case 5 was most likely related to the drop in hemoglobin.

2. The temporal presentation of case 6 was consistent with ribavirin-induced hemolytic anemia which might have induced this patient's chest pain and dyspnea. This case, again, underlines the potentially serious complications with ribavirin + IFN therapy in patients with significant cardiovascular risks.

2.7.3. Death

Patient # 20-06 (placebo + IFN arm), a 37-year-old woman with a long history of drug abuse, died from illicit drug overdose on day 291 (during the follow-up period). Although the investigator considered the event related to treatment, the applicant did not consider the death related to treatment.

Reviewer's Comment

A review of CRF showed that the patient developed new onset of moderate depression around treatment week 12 and was placed on antidepressant. Depression was noted at visits of weeks 16 and 20. The patient completed the treatment period. However, she missed several subsequent follow-up visits. Although no depression was noted by the investigator, the "Quality of Life" survey at week 12 was indicative of depression.

This patient was lost to follow-up until day 306 when the investigator learned that she had reportedly expired from "illicit" drug overdose. The investigator thought that the death was "possibly" related to treatment.

Of note was the fact that this patient's CRF contained records of adverse events for a follow-up visit dated 2 weeks after her demise. A complete examination of her medical records is still pending at the time this review was prepared since the applicant has not provided the requested records.

2.7.4. Laboratory Abnormalities**2.7.4.1. Hematological Abnormalities**

Interferon therapy has been linked to leukopenia, neutropenia, thrombocytopenia and, to a lesser degree, anemia. Ribavirin toxicity is primarily hemolytic anemia with a concomitant rise in bilirubin. These laboratory abnormalities are summarized in Table 2.7.4.1.A. Brief reviews on these parameters are given below.

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Table 2.7.4.1.A. Summary of Important Laboratory Abnormalities

Laboratory Parameter	Number (%) of Patients	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
Hemoglobin (g/dL)		
9.5 - 10.9 (grade 1) ¹	23 (24)	1 (1)
8.0 - 9.4 (grade 2)	1 (1)	-
Leukocyte count (x 10 ⁹ /L)		
2.0 - 2.9 (grade 1)	32 (34)	6 (6)
1.5 - 1.9 (grade 2)	2 (2)	1 (1)
Neutrophil count (x 10 ⁹ /L)		
1.0 - 1.49 (grade 1)	30 (32)	30 (31)
0.75 - 0.99 (grade 2)	11 (12)	6 (6)
0.5 - 0.74 (grade 3)	6 (6)	-
< 0.5 (grade 4)	-	2 (2)
Platelet count (x 10 ⁹ /L)		
70 - 99 (grade 1)	6 (6)	6 (6)
50 - 69 (grade 2)	1 (1)	3 (3)
Total bilirubin (mg/dL)		
1.5 - 3.0 (grade 1)	12 (13)	3 (3)
3.1 - 6.0 (grade 2)	3 (3)	-

¹ WHO grading criteria

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.6)

Hemoglobin Levels

Hemoglobin levels in the ribavirin + IFN treatment group began to drop at week 1 of treatment period to nadir by week 4. Compensatory reticulocytosis was noted in these patients. Table 2.7.4.1.B summarizes the maximum decreases from baseline in hemoglobin levels during the treatment period. The mean hemoglobin decrease for patients in the ribavirin + IFN group was 2.6 g/dL. In contrast, patients in the placebo + IFN had a mean decrease of hemoglobin of 0.8 g/dL. Hemoglobinemia persisted until the end of treatment period. By week 4 of the follow-up period, the hemoglobin returned to normal levels in most patients.

Table 2.7.4.1.B. Summary of Maximum Hemoglobin Decreases During Treatment Period

Hemoglobin Decrease (g/dL)	Number (%) of Patients	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
No change	-	2 (2.1)
> 0 to 1	5 (5.3)	35 (36.5)
> 1 to 2	24 (25.3)	50 (52.1)
> 2 to 3	35 (36.8)	8 (8.3)
> 3 to 4	24 (25.3)	1 (1.0)
> 4	7 (7.4)	-
Missing data	1	-

(Source: NDA 20-903, Protocol No. I95-145, Facsimile Correspondence dated 3/20/98)

Reviewer's Comment

Ribavirin-induced hemolytic anemia occurred in a relatively short period of time (1 - 4 weeks) after commencement of treatment. Therefore, it may pose clinical risks for patients with underlying hematologic, cardiovascular and pulmonary disorders.

White Blood Cell Counts

Reduction of WBC counts were observed in patients on both treatment arms. The mean baseline WBC counts were the same for both treatment arms ($6.6 \times 10^9/L$). The mean maximum WBC reductions during treatment period were $3.2 \times 10^9/L$ and $2.5 \times 10^9/L$ for patients on the ribavirin + IFN arm and placebo + IFN arm, respectively. The WBC counts reverted to normal levels in 4 weeks following cessation of therapy. The maximum WBC decreases during treatment period are summarized in Table 2.7.4.1.C.

Table 2.7.4.1.C. Summary of Maximum WBC Decrease During Treatment Period

WBC Decrease	Number (%) of Patients	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
No decrease	1 (1.0)	2 (2.1)
<25% of baseline	9 (9.4)	16 (16.7)
25 - 50% of baseline	46 (47.9)	67 (69.8)
50 - 75% of baseline	38 (39.6)	11 (11.5)
> 75% of baseline	2 (2.1)	-

(Source: NDA 20-903, Protocol No. I95-145, Facsimile Correspondence dated 3/20/98)

The baseline absolute neutrophil counts (ANC) were $3.8 \times 10^9/L$ and $3.7 \times 10^9/L$ for the IFN + ribavirin arm and placebo + IFN arm, respectively. The mean maximum ANC reductions during treatment period were $2.2 \times 10^9/L$ and $2.0 \times 10^9/L$, respectively. The applicant reported no significant increase in infection rate among patients on both treatment arms.

Reviewer's Comments

1. While ribavirin did not increase the neutropenic effects of interferon treatment, it appeared that ribavirin might have potentiated interferon-induced leukopenia. Results from Table 2.7.4.1.C showed that a higher proportion of patients on the ribavirin + IFN arm exhibited high-grade (50 - 75% reduction below baseline) leukopenia, compared to that of placebo + IFN arm.

2. Significant suppression of WBC counts and neutropenia associated with treatment drugs may potentially expose patients to higher risk of infections. Therefore, patients with preexisting immune deficiency conditions should be followed closely during treatment.

Platelet Counts

Treatment with ribavirin + IFN had negligible effect on overall platelet counts. Mean baseline platelet count was similar for both treatment arms ($220 \times 10^9/L$). The mean nadir platelet counts were $171 \times 10^9/L$ and $158 \times 10^9/L$ for the ribavirin + IFN arm and placebo + IFN arm, respectively. No untoward effects due to treatment-induced thrombocytopenia were observed.

Reviewer's Comment

Ribavirin treatment did not influence the incidence of interferon-induced thrombocytopenia in study patients.

Thyroid Abnormality

Autoimmune diseases with thyroid abnormality being most common were previously reported with interferon therapy. In this study, the proportions of patients with treatment-emergent TSH abnormalities were comparable for both treatment arms (approximately 2 - 3%). Of those who enter the study without thyroid abnormalities, 3 patients on the placebo + IFN arm and none on the ribavirin + IFN arm developed thyroid abnormalities requiring dose modification or treatment.

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2.7.4.2. Laboratory Abnormalities Associated with Premature Discontinuation of Treatment

The following case of laboratory abnormality resulting in premature discontinuation of treatment was also described in section 2.7.2.3 above.

Patient # 27-01 (ribavirin + IFN arm), a 76-year-old woman, experienced decreased hemoglobin level from baseline between weeks 4 to 20. She also experienced chest pain and dyspnea thought to be possibly related to anemia and was discontinued from the study on day 167. Her follow-up hemoglobin level at week 4 of the follow-up period returned to 11.5 g/dL.

2.7.5. Dosage Modification due to Adverse Events and Laboratory Abnormalities

Approximately 6% (5/96) of patients on the placebo + IFN arm and 23% (22/96) of patients on the ribavirin + IFN arm underwent dosage modifications because of adverse events and/or laboratory abnormalities. Table 2.7.5.A summarizes the reasons for dosage modifications. The relative frequencies of dosage modifications with respect to both drugs, ribavirin/placebo alone, or interferon alone are summarized in Table 2.7.5.B.

Table 2.7.5.A. Summary of Reasons for Dosage Modifications

Reason	Number (%) of Patients	
	Ribavirin + IFN (n = 96)	Placebo + IFN (n = 96)
Total	22 (23)	6 (6)
- Body as a whole	1 (1)	3 (3)
- Hypothyroidism	1 (1)	1 (1)
- Nausea/vomiting/dyspepsia	4 (4)	1 (1)
- Cardiac pain	-	1 (1)
- Hyperbilirubinemia	1 (1)	-
- Psychiatric ¹	4 (4)	-
- Sinus infection	1 (1)	-
- Urinary tract infection	1 (1)	-
- Anemia	7 (7)	-
- Neutropenia	2 (2)	-

¹ Includes depression, emotional lability, anxiety, irritability.

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.6)

Table 2.7.5.B. Types of Dosage Modifications

Dosage Modification	Number of Events	
	Ribavirin + IFN	Placebo + IFN
- Both drugs	16	2
- Ribavirin/placebo alone	14	2
- IFN alone	4	2

(Source: NDA 20-903, Protocol No. I95-145, Vol. 3.6)

Reviewer's Comment

In previous interferon trials for chronic hepatitis C, reduction in interferon dosage were reported in 10 - 40% of patients because of side effects. This study reported 6%. This was probably due to the higher ability to tolerate interferon therapy in these interferon-experienced patients

2.7.6. Treatment Discontinuations

According to the applicant, 2 (2%) patients in the interferon alpha-2b plus placebo arm and 4 (4%) in the interferon alpha-2b plus ribavirin arm were withdrawn from the study during the 24-week treatment phase. FDA analysis showed a total of 5 premature discontinuations in the interferon alpha-2b plus ribavirin arm. Four of these cases were due to adverse events related to IFN and/or ribavirin treatment, and 1 case due to non-compliance. During the follow-up period, 2 additional patients in each treatment arm discontinued the study due to loss of follow-up or death. These cases are summarized in Table 2.7.9.

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Table 2.7.6. Summary of Treatment Discontinuations

Reason for Discontinuation	Number of Patients	
	Ribavirin + IFN (n=96)	Placebo + IFN (n=96)
Treatment Period		
Total	5	2
- Insomnia/irritability	-	1
- Suicidal ideation/emotional lability	-	1
- Anorexia/depression	1	-
- Dyspnea	1	-
- Depression/emotional lability/dizziness	1	-
- Anemia/chest pain/dyspnea	1	-
- Non-compliance	1	-
Follow-up Period		
Total	2	2
- Loss to follow-up	2	1
- Death	-	1

(Source: FDA analysis of NDA 20-903, Protocol No. I95-145)

2.7.7. Overdosage Exposure

The applicant reported one patient (# 20-04) taking 1600 mg of ribavirin on two occasions after missing his daily doses. He reported back pain, myalgia, headache and fatigue in the first incidence and none in the second. No laboratory evidence of significant hemoglobin changes were noted. The patient has since reportedly remained asymptomatic.

2.7.8. Pregnancy

The applicant provided updated pregnancy data for this study in a safety update report (4/1998). Four pregnancies were reported, one in a study participant, and 3 in partners of study patients. These cases are summarized below:

Case 1. Patient # 13-07 (ribavirin + IFN arm) conceived during the follow-up period (week 10). She voluntarily terminated the pregnancy.

Case 2. Partner of patient # 19-01 (ribavirin + IFN arm) conceived 1 week prior to study commencement. She delivered a healthy female.

Case 3. Partner of patient # 17/BEL (ribavirin + IFN) conceived 3.5 months after the start of study drugs. Report on the outcome of this pregnancy was pending at the time of this safety update.

Case 4. Partner of patient # 22-03 (placebo + IFN) conceived approximately 4 - 5 months in the follow-up period. Report on the outcome of this pregnancy was pending at the time of this safety update.

2.8. Efficacy Outcomes

Comprehensive efficacy analyses can be found in the Biostatistical Review section by Dr. G. Soon. The following sections present some overviews on the virological, histological, biochemical responses for both treatment arms and the overall response rate.

2.8.1. Virological Response

The proportions of patients with HCV RNA measurements below limit of quantification at each evaluation time point during treatment period (weeks 4, 12, 24) and during follow-up period (weeks 36, 48) are summarized in Table 2.8.1.A. Although approximately 83% of patients on the ribavirin + IFN arm had viral suppression below limit of quantification at the end of treatment (week 24), this proportion dropped to about 52% by the end of the follow-up period (week 48). On the other hand, a sizable percent (45%) of patients on the placebo + IFN achieved virological response at the end of treatment. However, the sustained response rate at the end of follow-up was poor (5%).

Table 2.8.1.A. Proportions of Patients with HCV RNA below Limit of Quantification¹ at All Measured Time Points

Treatment Arm	Proportion (Number) of Patients				
	Treatment Period			Follow-up Period	
	Week 4	Week 12	Week 24	Week 36	Week 48
Ribavirin + IFN	30.2% (29/96)	78.1% (75/96)	83.3% (80/96)	53.1% (51/96)	52.1% (50/96)
Placebo + IFN	13.5% (13/96)	37.5% (36/96)	44.8% (43/96)	9.4% (9/96)	5.2% (5/96)

¹ Patients with missing HCV RNA results were counted as treatment failure.

(Source: FDA analysis of NDA 20-903, Protocol No. I95-145)

The proportions of patients with sustained virological response (i.e., those with HCV RNA levels below the limit of quantification from the end of treatment to the end of follow-up period) and non-sustained virological responders are summarized in Table 2.8.1.B. Virtually all sustained virological responders achieved HCV RNA suppression to below the limit of quantification by week 12 of treatment period.

Table 2.8.1.B. Summary of Virological Response

Virological Response	Proportion (Number) of Patients	
	Ribavirin + IFN	Placebo + IFN
Sustained response	46.9% (45/96)	5.2% (5/96)
Non-sustained response	53.1% (51/96)	94.8% (91/96)
Time to sustained response		
- By week 4	56.5% (26/45)	80.0% (4/5)
- By week 12	97.8% (44/45)	100.0% (5/5)

¹ Patients with missing HCV RNA results were counted as non-responders.

(Source: FDA analysis of NDA 20-903, Protocol No. I95-145)

Exploratory analysis on HCV genotypes (1a, 1b, 2, 3a) and virological response is summarized in Table 2.8.1.C. Genotypes 1, 2, and 3 are the most common HCV subtypes in patients from Europe and the USA. Genotypes 1a and 1b are associated with poor IFN treatment response in previous studies. The sustained response rate in placebo + IFN patients with genotype 1a or 1b was approximately 6% or less. Patients with these genotypes on the ribavirin + IFN arm had higher sustained response rate of approximately 30%.

Table 2.8.1.C. HCV Genotypes and Virological Response

HCV Genotype	Proportion (Number) of Patients			
	Sustained Responders		Non-sustained Responders	
	Ribavirin + IFN	Placebo + IFN	Ribavirin + IFN	Placebo + IFN
1 (total)	29.6% (16/54)	3.8% (2/52)	70.4% (38/54)	98.1% (51/52)
- 1a	30.0% (3/10)	0.0% (0/10)	70.0% (7/10)	100.0% (10/10)
- 1b	30.6% (11/36)	6.1% (2/33)	69.4% (25/36)	93.9% (31/33)
2 (total)	77.8% (7/9)	5.3% (1/19)	22.2% (2/9)	94.7% (18/19)
3a	67.7% (21/31)	9.1% (2/22)	32.3% (10/31)	90.9% (20/22)

(Source: FDA analysis of NDA 20-903, Protocol No. I95-145)

Reviewer's Comments

1. Although the HCV RNA assay used by the applicant was considered by FDA as an investigational quantitative methodology, the applicant provided quantitative data on HCV RNA levels. Exploratory analysis using these data showed that the mean baseline HCV RNA levels of patients who showed sustained virological response were approximately 1.4×10^5 copies/mL ($n = 5$) and 2.8×10^6 copies/mL ($n = 45$) for the placebo + IFN group and ribavirin + IFN group, respectively. The mean baseline HCV RNA levels among the non-sustained virological

responders were 4.4×10^6 copies/mL ($n = 91$) for the placebo + IFN group and 4.0×10^6 copies/mL ($n = 51$) for the ribavirin + IFN group. These facts indicated that patients with low baseline HCV RNA levels appeared to have better virological response.

2. Quantitative HCV RNA data also showed that among patients in the IFN + ribavirin group, mean baseline HCV RNA levels for those who achieved viral suppression to below limit of quantification by week 4 and week 12 were 2.4×10^6 copies/mL ($n = 26$) and 3.2×10^6 copies/mL ($n = 19$), respectively. Therefore, lower baseline HCV RNA levels were associated with faster rate of viral suppression.

3. Based on the two observations above, it appeared that lower baseline viremia was associated with earlier suppression of viremia by treatment and sustained virological response.

4. While the end-of-treatment response rate (45%) of the placebo + IFN arm in this study was comparable to results of other interferon monotherapy trials (approximately 30-40%), the 6-month post-treatment virological response was only about 5%. This response rate was lower than what has been reported in previous 6-month interferon trials, i.e., 10-20%. This was probably due to the fact that the study enrolled interferon-treatment relapsed patients.

5. It is unknown whether patients with no virological response developed resistant strains of HCV or whether drug therapy was suboptimal due to poor compliance.

2.8.2. Histological Response

Complete pairs of pre-treatment and post-treatment biopsies were available for 81.2% (78/96) and 77.1% (74/96) of patients on the ribavirin + IFN arm and placebo + IFN arm, respectively.

Mean changes from baseline (post-treatment score - pre-treatment score) of Knodell HAI scores by individual component for sustained virological responders and non-sustained virological responders in each treatment group are summarized in Table 2.8.2. Patients with sustained virological response had greater improvement of Knodell HAI scores for the necroinflammatory components (I, II, and III). The mean changes in fibrosis score did not indicate significant histological variation between the pre-treatment and post-treatment biopsies in both treatment arms.

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Table 2.8.2. Mean Change from Baseline of Knodell HAI Scores

Knodell HAI Component	Mean Change from Baseline ¹			
	Ribavirin + IFN		Placebo + IFN	
	Sustained virological responders (n = 42) ²	Non-sustained virological responders (n = 36) ²	Sustained virological responders (n = 4) ²	Non-sustained virological responders (n = 70) ²
I (periportal necrosis)	-1.6	-0.5	-1.7	-0.3
II (intralobular degeneration)	-1.3	-0.6	-1.7	0.2
III (periportal inflammation)	-1.2	-0.1	-1.0	-0.3
IV (fibrosis)	-0.2	-0.1	0.5	-0.1
Total (I+II+III+IV)	-4.3	-1.4	-4.0	-0.6

¹ Negative value indicates improvement.

² Only patients with paired pre-treatment and post-treatment biopsies were included in analysis.

(Source: FDA analysis of NDA 20-903, Protocol No. I95-145)

The distributions of mean changes from baseline of Knodell HAI total scores for sustained virological responders and non-sustained virological responders in the ribavirin + IFN group are schematically displayed in Figure 2.8.2.A. The majority of patients (78.5%) with sustained virological response had improved liver biopsies, using the applicant's arbitrary cut-off of Knodell HAI score of ≤ -2 . A small number of these patients (5.0%) had worse post-treatment liver biopsy. On the other hand, the distribution Knodell HAI scores among non-sustained virological responders showed a bimodal distribution. Approximately 58.5% of these patients had either no significant change or worse liver biopsy findings. Among those with significantly worsened biopsies (i.e., Knodell HAI score change of ≥ 3), none had significant progression of fibrosis. In addition, a smaller group of patients (41.8%) had histological improvement with a mean histological improvement of approximately 4 points.

The distribution of mean changes from baseline of Knodell HAI scores for the placebo + IFN group is shown in Figure 2.8.2.B. The majority of patients (94.8%) on this arm had no sustained virological response. However, approximately 38.6% of these patients exhibited some degree of histological improvement that could be attributed to interferon effect. A histogram for the sustained virological responders is not included in Figure 2.8.2.B since there were only 4 patients in this group.

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Figure 2.8.2.A. Distribution of Mean Change from Baseline of Knodell HAI Score in the Ribavirin + IFN group

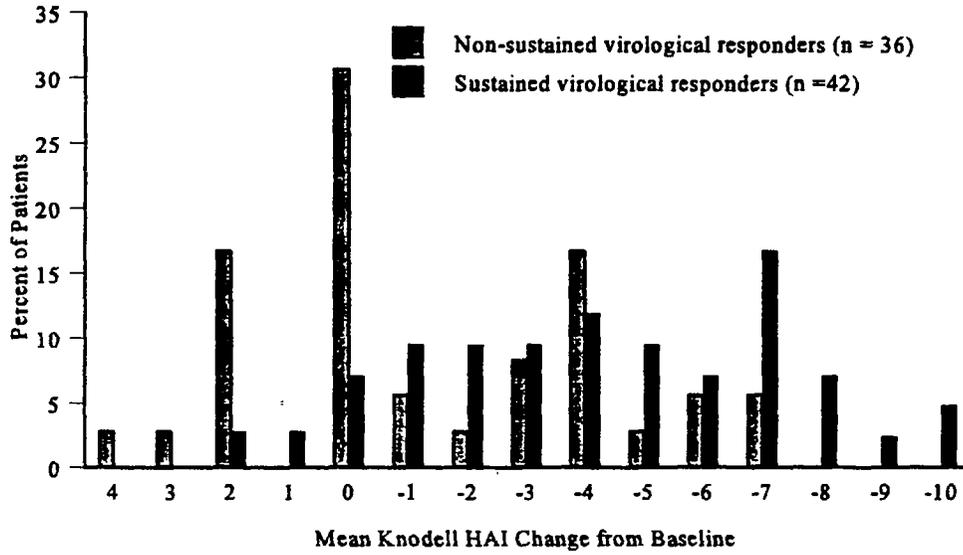
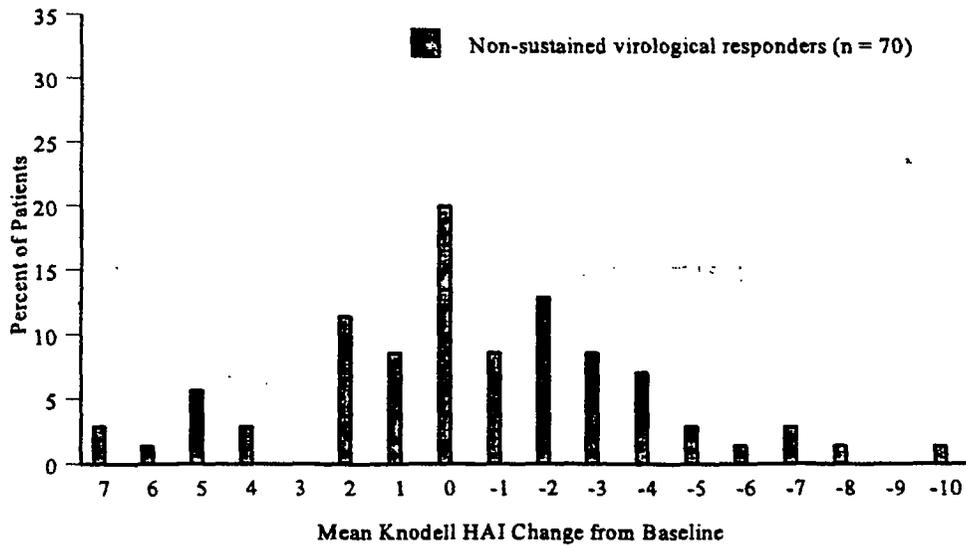


Figure 2.8.2.B. Distribution of Mean Change from Baseline of Knodell HAI Score in the Placebo + IFN group



Reviewer's Comments

1. *The applicant chose to use Knodell necroinflammatory score (i.e., sum of components I + II + III) in their interpretation of histological findings. In this review, Knodell total score (i.e., summation of both necroinflammatory (component I + II + III) and fibrosis scores (component IV)) was used to assess the histopathological changes over time between the baseline and post-treatment biopsies. The overall results using these different HAI scores did not differ significantly since the majority of patients did not exhibit progression of fibrosis. However, it is important to note that the duration of post-treatment follow-up (24 weeks) was relatively short to appreciate any differential progression of fibrosis between treatment arms or between subgroups of patients. Long-term follow-up histopathological data will be needed to assess durability of therapeutic effect.*

2. *According to the applicant, a change from baseline of 2 points (or units) or more in the Knodell HAI "inflammation" score indicates histological improvement. Although this arbitrary cut-off is reasonable, there is no evidence in clinical literature to support its clinical significance. A more useful approach to assessment of histological response can be achieved by examining the overall distribution of hepatic histological abnormalities (based on HAI score) for each subgroup of patients.*

3. *While patients in the ribavirin + IFN group showed histologic improvement (mean change from baseline of - 2.9 points) on post-treatment liver biopsies, the magnitude of histological improvement in the placebo + IFN population did not appear significant (mean change of - 0.8 point). Since the number of sustained virological responders in the placebo + IFN group was small (n = 4), the post-treatment improvement in Knodell HAI score for this group could not be meaningfully evaluated. However, in the ribavirin + IFN group, the difference between mean changes from baseline in Knodell HAI of sustained virological responders (- 4.6 points) and non-sustained virological responders (- 1.4 points) from a baseline of 7.9 points was statistically significant. These data showed that sustained virological response was accompanied by histological improvement. It is worth emphasizing that a small proportion of patients without sustained virological response still had histological improvement (Figure 2.8.2.A).*

4. *The data also showed that interferon alone produced histological improvement in approximately 1/3 of patients. The overall magnitude of improvement, however, was less than that seen in combination treatment.*

5. *Among the 6 patients with histological evidence of cirrhosis on pre-treatment biopsies, one did not have follow-up biopsy (ribavirin + IFN), and one appeared to have biopsy sampling error (placebo + IFN). One patient (ribavirin + IFN) had improvement of necroinflammatory (I + II + III) scores. The remaining cases were essentially unchanged. All but one patient on the placebo + IFN arm did not have sustained virological response.*

6. It was noted that one study center (I95-145-09) enrolled 6 patients. Among these, 5 patients did not have post-treatment liver biopsy. One patient had suboptimal biopsy that was not evaluable. With the exception of this site, other centers did not encounter significant difficulty with obtaining post-treatment biopsies.

2.8.3. Biochemical Response

Table 2.8.3 summarizes the relationship among patients who demonstrated sustained virological response and those who failed to achieved sustained virological response and normalization of elevated ALT levels. The majority of sustained virological responders in both treatment groups appeared to have resolution of elevated ALT levels at the end of treatment period and at the end of follow-up period. Among the non-sustained virological responders, the majority had normalization of ALT levels at the end of treatment. However, at the end of follow-up period, the ALT levels in most of these patients reverted back to abnormal range.

Table 2.8.3. Correlation between Normalized End-of-Treatment/End-of-Follow-up ALT levels and Virological Response

Virological Response	Proportion (number) of Patients with Normalized ALT Levels ¹			
	At end-of-treatment (week 24)		At end-of-follow-up (week 48)	
	Ribavirin + IFN	Placebo + IFN	Ribavirin + IFN	Placebo + IFN
Sustained response	97.8% (44/45)	100.0% (5/5)	97.8% (44/45)	100.0% (5/5)
Non-sustained response	76.5% (39/51)	54.9% (50/91)	17.6% (9/51)	13.2% (12/91)

¹ Patients with missing virological data were counted as non-responders.

(Source: FDA analysis of NDA 20-903, Protocol No. I95-145)

Reviewer's Comment

There was a high concordance between sustained virological response and normalization of ALT levels at the end of treatment (week 24) and at the end of follow-up period (week 48). This implies that ALT levels can serve as a useful marker in post-treatment monitoring of those patients who demonstrate virological response at the end of treatment.

2.8.4. Overall Response

As defined in the protocol, the primary efficacy endpoints were the overall response (based on composite endpoint of sustained virological response and ≥ 2 -point improvement in liver biopsy Knodell HAI "inflammation" score). Using "maximum likelihood estimate" model, the applicant reported 42.7% overall response rate in the ribavirin + IFN group and 5.2% in the placebo + IFN group. However, when patients with missing virological and biopsy data were considered as

nonresponders in the analysis, the overall response rates were 40.6% (39/96) and 4.2% (4/96) for the ribavirin + IFN arm and the placebo + IFN arm, respectively. Results of overall response are summarized in Table 2.8.4.

Table 2.8.4. Overall Response Rate Analysis

Overall Response Rate	Ribavirin + IFN	Placebo + IFN	p value
Applicant's results			
- Maximum likelihood estimate ¹	42.7%	5.2%	< 0.001
- Conservative analysis ²	40.6% (39/96)	4.2% (4/96)	< 0.001
FDA result ^{2,3}	36.5% (35/96)	4.2% (4/96)	< 0.001

¹ Histological analysis based on Knodell HAI "inflammation" score (I + II + III)

² Patients with missing virological or biopsy data were counted as non-responders.

³ Histological analysis based on Knodell HAI total score (I + II + III + IV)

Reviewer's Comments

1. FDA analysis of overall response rate included all patients with HCV RNA below limit of quantification at the end of treatment and during follow-up period (i.e., HCV RNA measurements < 100 copies/mL at weeks 24, 36 and 48) who had improved Knodell HAI total score (component I, II, III, and IV) of ≥ 2 . Please see also Reviewer's Comment # 1, section 1.9.2.

2. Although favorable virological and histological results appear to confirm short-term treatment benefit of ribavirin + IFN, the long-term clinical outcomes (e.g., disease progression, quality of life) remain unknown.

2.8.5. Gender Analysis

Analyses based on gender did not show significant difference in virological and histological response rates between male and female patients in this study. Please refer to Dr. Soon's Biostatistical Review section for additional details.

3. REVIEWER'S FINAL ASSESSMENT

3.1. Risks

The principal toxicity-associated risks of combination ribavirin/interferon alpha-2b therapy are consistent with the known profiles of each drug in monotherapy. Interferon treatment has been associated with "flu-like" symptoms, fatigue, neuropsychiatric effects, bone marrow suppression, and alopecia. Other severe side effects occurring in less than 2% of patients include autoimmune disease, seizure, acute cardiac and renal failure. The most clinically important adverse even in ribavirin treatment is hemolytic anemia.

It should be reemphasized that the patient population in this study have had successful prior treatment experiences with interferon. Therefore, they may have tolerated therapy better than interferon-naive patients. The majority of patients in both treatment groups (85% in placebo + IFN vs. 86% in ribavirin + IFN) experienced "flu-like" symptoms of headache, fever, myalgia, fatigue and asthenia frequently observed with interferon alpha-2b therapy. Most of these were mild to moderate in intensity and appeared to respond to symptomatic treatments. None of the symptoms required dosage modifications or discontinuation of treatment.

Significant proportions of patients (43% in placebo + IFN group, 44% in ribavirin + IFN group) reported neuropsychiatric adverse events, with insomnia, irritability and depression leading the list. Their frequencies were comparable in both treatment groups. Approximately 2% of patients prematurely discontinued study participation due to neuropsychiatric adverse events. Depression occurred in 8% of patients on the placebo + IFN arm and 10% on the ribavirin + IFN arm. One patient (ribavirin + IFN arm) had severe depression with suicidal ideation. Of note, one patient (placebo + IFN arm) developed depression during treatment and subsequently died of illicit drug overdose.

Virtually all patients on both treatment arms experienced mild to moderate interferon-induced bone marrow suppression evidenced by leukopenia, neutropenia and thrombocytopenia. Data from this study suggested a contributory role of ribavirin to leukopenia; however, ribavirin did not potentiate neutropenia. Leukopenia may potentially expose patients with preexisting immune deficiency conditions to higher risk of infection during therapy. Significant thrombocytopenia was observed in a small proportion of patients (< 2%), although no clinical complications were reported. However, these hematologic abnormalities resolved after cessation of therapy.

Although a relatively small number of patients developed thyroid disorders (3% in the placebo + IFN group, 2% in the ribavirin + IFN group), most of these patients had to have interferon dosage modification, or treatment for these conditions.

Ribavirin-induced hemolytic anemia occurred in a relatively short period of time (1 - 4 weeks) after commencement of treatment. Approximately 57% of patients in the ribavirin + IFN had hemoglobin decrease of more than 2 g/dL and 7% of these patients had greater than 4 g/dL decrease of hemoglobin. Combination treatment with ribavirin/interferon alpha-2b may, therefore, pose clinical risks for patients with underlying hematological disorders. In addition, anemia may exacerbate cardiovascular and pulmonary conditions in patients with significant preexisting diseases.

Ribavirin has been shown to have abortifacient, embryotoxic and/or teratogenic effects in animals (see Pharm/Tox Review section). The potential human risks are of concern for patients who become pregnant during therapy. Therefore, women of child bearing age should not receive treatment unless adequate contraception is practiced

Ribavirin/interferon alpha-2b treatment should be used with caution in patients with underlying renal insufficiency since ribavirin clearance has been shown to be reduced in patients with significant renal dysfunction (see Biopharm Review section).

3.2. Benefits

This study demonstrated benefits of ribavirin/interferon alpha-2b combination therapy in a limited group of patients with chronic hepatitis C who showed evidence of relapse following prior interferon therapy. Efficacy data showed a greater proportion of patients on combination therapy (47%) with viral suppression (HCV RNA levels below limit of quantification at the end of treatment, and during the 24-week follow-up) than those on interferon monotherapy (5%). In addition, virological response was accompanied by histological improvement in post-treatment liver biopsy. Most, if not all, patients with sustained virological response also had normalization of ALT levels. While the results showed strong concordance in terms of virological, histological and biochemical responses, the long-term durability of treatment response and its effect on disease progression remains unknown.

3.3. Conclusion

The risks associated with ribavirin/interferon alpha-2b therapy can be reduced or managed by appropriate patient selection and close clinical assessment and laboratory monitoring. The study shows that this combination therapy in alpha-interferon relapse patients produces greater proportion of patients with virological response accompanied by histological improvement and normalization of ALT 6 months after treatment. However, the durability of treatment effect and the long-term clinical outcome on disease progression remain unknown.

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MO/DAVDP/ODEIV/CDER/FDA/HFD-530

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