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Application Number 20-903

CLINICAL REVIEW(S)

NDA 20-903

DRAFT 5/14/98

CLINICAL REVIEW

Date submitted: December 3, 1997
Date received: December 5, 1997
Date assigned: December 8, 1997
Date completed: May 22, 1998

1. General Information

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Drug:
Generic: ribavirin
Trade: Rebetol™
Chemical: 1-β-D-Ribofuranosyl-1-H-1,2,4-triazole-3-carboximide

Route: Oral

Dosage Form: Capsule

Strength: 200 mg

Proposed Indication: Treatment of chronic HCV infection in patients with compensated liver disease who have relapsed following previous interferon therapy

Related INDs:

Related NDAs: 20-442 (ribavirin for hepatitis C virus infection)
18-859 (aerosolized ribavirin for respiratory syncitial virus)

Related PLAs: Intron® A (interferon alfa-2b-recombinant)

Related Documents: *Medical Officers review dated*: March 5, 1996
End-of-phase two letter dated: March 7, 1996
Minutes of Pre-NDA meeting dated: June 30, 1997
Responses to requests for information dated: December 18, 1997, January 12, 1998, January 13, 1998, January 15, 1998, January 16, 1998, January 20, 1998, March 6, 1998, March 20, 1998, March 26, 1998, April 17, 1998
4-Month Safety Update dated: March 26, 1998
Memorandum from DSI dated: May 4, 1998

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2. Summary

The applicant has submitted results from two double-blind, randomized, placebo-controlled trials (C95-144 and I95-145) of INTRON® A (Interferon alfa-2b-recombinant) with REBETOL™ (ribavirin) Capsules or placebo in patients who relapsed, as evidenced by elevated ALT levels, following a previous course of alfa-interferon therapy. In these trials, 345 male and female adult patients with compensated liver disease were randomized to receive treatment with INTRON A 3 MIU thrice weekly with either ribavirin 600 mg twice daily (INTRON A + ribavirin) or placebo (INTRON A + placebo) for 24 weeks followed by 24 weeks of off-therapy follow-up. The primary efficacy endpoints were based on virologic response and improvement in liver histology.

Sustained virologic response was defined as HCV-RNA below the limit of quantification of the assay by the end of therapy that was maintained throughout the follow-up period. The response rates for this endpoint were 42% and 48% in the combination arms of the two studies. This compared to a 3.9% and 5.2% sustained virologic response in the two INTRON A + placebo-treated groups. In both studies, all of patients in the INTRON A + ribavirin treatment groups who were sustained virologic responders had achieved their initial virologic response by week 12 of therapy.

Complete sets of pre- and post-study liver biopsies were obtained in patients in both studies. Histologic improvement, defined as $\geq$2 point improvement in components I+II+III of the Knodell HAI score were 62% in the INTRON A + ribavirin group and 42% in the INTRON A + ribavirin and INTRON A + placebo arms of study C95-144. In study I95-145, the histological improvement rates were 62% and 42% for the two treatment groups, respectively. Although fibrosis (component IV) is an important marker of disease activity, inclusion of this parameter in the analysis did not appreciable affect the histologic response rates seen in these studies. These data further support the notion that fibrosis did not worsen during the studies.

Patients who achieved both a sustained virologic response and histologic improvement were considered overall responders. The results of study C95-144 demonstrated that a significantly higher proportion of patients treated with INTRON A + ribavirin had an overall response compared to patients treated with INTRON A + placebo; 30% versus 3%, respectively. The results of study I95-145 were similar; 35.4% of those treated with the combination were overall responders compared to 4.2% of INTRON A + placebo-treated patients.

Early ALT response (by week 12) was correlated with sustained virological response in both studies. Also, a normal ALT value at week 48 was correlated with a HCV-RNA below the LOQ at week 48. Normalization of ALT did not correlate with histological response and generally underestimated the histological response to therapy.

Lower baseline HCV-RNA levels ($\leq$2 million copies/mL) and non-Genotype 1 virus were weakly correlated with a favorable response to therapy. However, neither baseline ALT levels, HCV-RNA levels, or Knodell HAI score were predictive of a response to therapy.

Safety evaluations of over 25,000 patients who received INTRON A + ribavirin between August 1995 and the present were included in the safety data base. There have been 23 deaths reported in this database.

Approximately 98% of patients in the two clinical trials experienced adverse events. The occurrence of serious psychiatric (depression and suicidal behavior), hematological (anemia) and cardiovascular (myocardial infarction) events, some of which were associated with death, indicate that patients appear to be at a significant risk for toxicity from this combination. These data reinforce the need for close monitoring of patients who will receive this combination. Patients with significant pre-existing cardiovascular, pulmonary, or psychiatric disease were excluded from these trials. Therefore, consideration should be given to excluding patients with significant pre-existing cardiovascular or psychiatric disorders from receiving this combination therapy.

Both agents are known to have adverse effects on pregnancy outcomes. Women of child bearing potential and their partners who become pregnant while receiving combination therapy will be at a significant risk for adverse birth outcomes Evaluation of the incidence and outcomes of pregnancies will be important as these agents enter general clinical use.

In conclusion, based on the data submitted in NDA 20-903, the combination of INTRON A + ribavirin was more effective than re-treatment with INTRON A alone for the treatment of HCV infection in patients with compensated liver disease who have relapsed following previous INTRON A monotherapy.

Adverse events occurred in nearly all of the patients in the two relapse studies. The types of events were consistent with those associated with either interferon or ribavirin therapy, although the frequency of events was generally higher in the combination arms of the two studies. The adverse events of primary concern were depression, associated with suicidal behavior, and anemia.

3. Background

3.1 Regulatory History

Ribavirin is a guanosine analogue that has *in vitro* antiviral activity against a number of different RNA viruses. The mechanism of action is unknown but several mechanisms have been suggested including depletion of intracellular triphosphate pools, inhibition of viral polymerase, inhibition of 5' capping, and inhibition of TH2 cytokines. Ribavirin enters the red blood cell and has an intracellular half-life of approximately 300 days.

Aerosolized ribavirin was approved in 1988, for the treatment of respiratory syncytial virus in infants.

Anemia is the most common adverse event in clinical trials of ribavirin. Ribavirin has also been demonstrated to be mutagenic, teratogenic and embryocidal in animal studies. Aerosolized ribavirin is currently labeled as Pregnancy Category X.

An NDA for oral ribavirin monotherapy for the treatment of chronic HCV infection was submitted by ICN Pharmaceuticals in May 1994. In November 1994, it was determined that the application was not approvable because oral ribavirin only normalized serum ALT levels in approximately 40% of patients, but did not have an effect on either HCV-RNA levels or liver histology. Further, once therapy was discontinued, the ALTs returned to pre-treatment levels.

Phase III protocols of ribavirin in combination with INTRON A were developed by
but were never initiated. In August 1995, oral ribavirin was licensed to Schering Corporation for further development for treating HCV infection. The rationale for development of ribavirin in combination with INTRON A was based on findings from a number of small pilot studies suggesting that a six month course of combination therapy was associated with sustained antiviral responses, as measured by reductions in HCV-RNA, ranging from 35-45% in patients naïve to interferon, and 30-40% in patients who had relapsed following previous interferon therapy.[1,2,3] These studies did not provide data on histologic responses.

The IND for the combination of Intron A/oral ribavirin was filed in January 1996. The protocol for study C95-144 was submitted with the IND; comments were provided March 5, 1996. In addition to comments on the proposed protocol, a request for information about lower doses of ribavirin was forwarded to the applicant. A pre-NDA meeting was held on June 30, 1997, and the NDA was submitted December 4, 1997.

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[1]Brillanti S, Garson J, Foli M, et al. A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa resistant chronic hepatitis C. Gastroenterology 1994; 107:812-6.

[2]Chemello L, Cavaletto L, Bernardinello E, et al. Response to ribavirin, to interferon and to a combination of both in patients with chronic hepatitis C and its relation to HCV genotypes. Symposium on hepatitis C virus and related viruses. San Diego, CA; 1994:204 (abstract).

[3]Lai MY, Kao JH, Yang PM, et al. Combination therapy of interferon and ribavirin in patients with chronic hepatitis C. Symposium on hepatitis C virus and related viruses. San Diego, CA; 1994:197 (abstract).

3.2 Natural History and Treatment of Hepatitis C

Hepatitis C is a viral infection that accounts for 70% to 90% cases of viral hepatitis. The hepatitis C virus is a single-stranded, positive-sense RNA virus in the Flaviviridae family. At least six distinct genotypes and 30 subtypes have been identified.

It is estimated that 3.5-4 million persons in the United States are chronically infected with HCV. Approximately 150,000-200,000 acute new infections occur each year, about 25-30% of which are diagnosed. Hepatitis C infection accounts for 20% of cases of acute hepatitis, and accounts for approximately 12,000 deaths annually. Hepatitis C infection is now the leading cause of liver transplantation in the US.

HCV is transmitted primarily by the parenteral route. The risk of infusion-related hepatitis is in the range of 1 in 100,000 units transfused.

Infection with HCV is persistent. After initial exposure, HCV-RNA can usually be detected in the serum within 1-3 weeks. Within about 50 days almost all patients will develop liver cell injury, as shown by elevation of serum alanine transferase (ALT). The majority of patients are asymptomatic and anicteric. Twenty-five to 35% of patients develop symptoms such as fatigue, malaise, weakness, nausea, or anorexia, and become icteric. Fulminant liver failure is rare. Antibodies to HCV become detectable during the course of the illness; anti-HCV is detectable in 50-70% at the onset of symptoms and in 90% three months after onset of infection. HCV is self-limiting in 15% of cases with recovery characterized by disappearance of HCV-RNA and return of liver enzymes to normal. HCV genotypes 2 and 3, low serum HCV-RNA levels ($<1 \times 10^6$ copies/mL), and the absence of cirrhosis have been reported to be associated with more favorable responses to treatment with interferon monotherapy.(Consensus conference)

HCV infection is not easily cleared by the host's immunologic defenses. Thus, nearly 85% of patients fail to clear the virus by 6 months and develop chronic hepatitis with persistent viremia. The majority will have abnormalities in ALT levels that can fluctuate widely. Antibodies to HCV or circulating viral RNA is present in virtually all patients. Chronic hepatitis C is generally insidious, progressing, if at all, at a slow rate without signs or symptoms in the majority of patients during the first two decades after infection. Chronic hepatitis C infection leads to cirrhosis in about 20% of patients within two decades. Once cirrhosis is established, liver failure and portal hypertension can occur. Patients usually become jaundiced, and have ascities, variceal hemorrhage and encephalopathy. The rate of progression is highly variable. The relationship between ALT and disease severity, as judged by histology, is inconsistent.

Chronic hepatitis C infection is associated with increased risk of hepatocellular carcinoma (HCC). Most cases of HCV-related HCC occur in the presence of cirrhosis. HCC occurs more commonly in men than in women and in older than younger patients.

Data from one retrospective study of patients treated with interferon (3-6 MIU three times per week for 6-12 months) suggests that for patients with cirrhosis at entry, interferon therapy does not correlate with a reduced incidence of liver cancer or improved survival. The prognosis for these patients is poor, with a 5-year survival rate of only 50%.[4]

INTRON A® was approved for the treatment of chronic non-A, non-B hepatitis in February 1991. Intron A at a dose of 3 MIU TIW for six months produced responses (normalization of serum ALT and loss of detectable HCV-RNA) of 40-50%, and sustained responses of 15-20% in INTRON A naïve patients. Increasing duration of treatment to 12 months has generally not been associated with higher end of treatment biochemical or virological responses, but has increased the sustained responses to 20-30%.[5] In 1997, INTRON A was approved for 18 months of monotherapy; this regimen is associated with

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[4]Schlam SW, Fattovich G, Brouwer JT. Therapy of hepatitis C: patients with cirrhosis. Hepatology, 1997; 26:128S-132S.

[5]NIH Consensus Development Conference Panel Statement. Management of hepatitis C. Hepatology 1997;26(Suppl 1):2S-10S.

Flu-like symptoms such as fatigue, fever, headache, myalgia are most often reported adverse events associated with INTRON A use. Myelosuppression has also occurred with the administration of INTRON A. INTRON A is an abortifacient. Psychiatric disorders including depression, emotional lability, suicidal ideation and successful suicides have been reported in patients receiving INTRON A.

3.3 International Marketing Experience

Ribavirin is approved as an aerosol, capsule, oral solution, syrup, injectable and topical cream formulations in 48 countries. Ribavirin is currently approved for the treatment of HCV infection in Mexico and Egypt. INTRON A® is approved in 69 countries, including the United States, for the treatment of HCV infection.

3.4 Clinical Implications of Preclinical Studies

3.4.1 Chemistry

Please refer to Dr. Kambhampati's review. There were no issues of clinical concern in the Chemistry Review.

3.4.2 Microbiology

Please refer to Dr. Batulla's review for information about the antiviral activity of INTRON A and ribavirin. Serum HCV-RNA levels were determined by a central laboratory in serum using an experimental (research-based) assay. The lower limit of quantification for this assay was undefinable. Further, the mechanism of action of the combination against the hepatitis C virus remains unknown.

3.4.3 Pharmacology/toxicology

Please refer to Dr. Morse's review. Ribavirin has been shown to be teratogenic and embryocidal in animal studies, and is considered a potential human carcinogen. The interferons are known abortofacients. The data provided in the NDA were not sufficient to address the concern of ribavirin's potential carcinogenicity. Therefore, additional, post-marketing, studies will be necessary. (See section 12.0).

3.4.4 Biopharmaceutics

Please refer to Dr. Rajagapolan's Clinical Pharmacology review for information about the effects of food on the bioavailability of ribavirin, and information about administration of ribavirin to patients with renal impairment. Further, no formal drug interaction studies have been performed.

4.0 Materials Reviewed

This NDA contains 294 volumes; of which 111 comprise the clinical section. All volumes of the clinical section of the NDA were reviewed in detail with the exception of the data devoted to assessment of quality-of-life. The quality-of-life data was primarily reviewed by the Division of Drug Marketing, Advertising and Communications. (See)

The narratives and CRFs for deaths, serious adverse events and discontinuations that occurred in the two pivotal trials were reviewed. In addition, blinded safety data from two ongoing studies in interferon naïve patients and MedWatch forms for all deaths and serious adverse events that occurred during treatment and investigator-initiated protocols and open-label use were reviewed.

5.0 Summary of Clinical Section

Two trials were conducted in patients with chronic HCV infection who had relapsed, evidenced by an abnormal ALT within one year following the end of the most recent course of interferon therapy. Both trials, C95-144 and I95-145, were identical in the protocol design, duration of treatment, drug dosages used, and endpoints measured. The location of the study centers differ; study C95-144 was conducted in the United States and I95-145 was conducted in Europe, Canada, Australia and Israel.

Table 1. Summary of submitted principal studies

Study	Location	Enrolled (N)	INTRON A + Ribavirin	INTRON A + Placebo
C95-144	21 US sites	154	77	76
I95-145	31 Foreign sites	195	96	96

To support the safety of the combination, the applicant has submitted complete safety data from the above two trials, blinded 24 week safety data from two ongoing trials in interferon naïve patients, and a review of serious adverse events and deaths that have occurred during Schering-controlled and investigator-initiated treatment protocols, and open-label use.

6.0 Clinical Trial C95-144

"Interferon Alfa-2B (INTRON A) monotherapy versus Interferon Alfa-2B (INTRON A) + Ribavirin (Sch 18908) for treatment of relapse in patients with chronic hepatitis C."

6.1 Study Design

This was a phase III, prospective, randomized, double-blinded study designed to compare the safety and efficacy of the combination of INTRON A + ribavirin to INTRON A + placebo in patients with chronic HCV infection in patients who had relapsed, as evidenced by abnormal ALT levels within one year after showing a response to 1 or 2 courses of alfa-interferon (3 MU to 6 MU QOD or TID for 20 weeks to 18 months). Patients received treatment for 24 weeks followed by a 24-week off-therapy follow-up to determine durability of treatment response. The study was conducted between April 1, 1996 and October 27, 1997.

The study population included 153 adult patients who were randomly assigned to receive INTRON A 3 MIU TIW + ribavirin 1,000 or 1,200 mg/day (n=77) or INTRON A 3 MIU TIW + placebo (n=76). The dose of ribavirin was based on weight; patients weighing ≥75 kg received 600 mg BID and those weighing <75 kg received 500 mg BID.

Comment: The dosing regimen of INTRON A used in this study was the licensed regimen at the time the study was initiated. The ribavirin dose was based on the maximally tolerated dose that had been used in previous monotherapy studies. Dose ranging studies that were requested by the agency are in progress.

During treatment and post-treatment follow-up, ALT and HCV-RNA levels were to be monitored serially. In addition, histopathological comparisons of pre-treatment and post-treatment (obtained at week 48) liver biopsies were to be conducted by a central pathologist using components I+II+III of the Knodell Histology Activity Index[6] score. During the treatment phase, patients were assessed every 2 weeks for 8 weeks and

[6]The Knodell HAI composite score ranges from 0 to a maximum of 22. To obtain the composite score, liver biopsy is evaluated for periportal +/- bridging necrosis (category I), intralobular degeneration and focal necrosis (category II), portal inflammation (category III) and fibrosis (category IV). For each category, absence of activity, mild activity, moderate activity, and severe activity are attributed with numerical scores of 0, 1, 3, and 4, respectively. A score of 2 is not given. The composite score weighs heavily on category I (periportal +/- bridging hepatocellular necrosis) with maximum score of 10, whereas the highest scores for other

every 4 weeks thereafter for clinical adverse events and laboratory safety tests. Similar assessments were conducted during post-treatment follow-up at weeks 4, 8, 12 and 24.

Inclusion Criteria
Patients were eligible for enrollment if they had a positive serum hepatitis C virus by quantitative RT-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 Hgb > 12 g/dL and 13 g/dL for females and males, respectively; WBC $\geq$3,000/mm^3; platelets $\geq$100,000/mm^3; 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 or no evidence of hepatocellular carcinoma on ultrasound; negative HBsAg; negative HIV status; and adequate birth control practice.

Exclusion Criteria
Patients were excluded if they had other causes of liver disease, decompensated liver disease, were HIV or HBsAG positive. In addition, history of ribavirin use, active illicit intravenous drug use, pregnancy, breast-feeding, heavy alcohol consumption (>20 g/day), participation on other investigational therapy, were reasons for exclusion. Patients with a pre-existing psychiatric condition, especially severe depression or a history of severe psychiatric disorder; cardiovascular disorders including angina, congestive heart failure, recent myocardial infarction, severe hypertension, significant arrhythmias or an ECG showing clinically significant abnormalities; coexisting liver disease, and recipients of organ transplantation were not allowed to participate in this study.

Comment: The applicant enrolled a relatively healthy population of HCV infected patient with mild hepatic disease at entry who had all responded to a previous course of interferon monotherapy.

Randomization was stratified according to three criteria: presence or absence of cirrhosis, serum HCV-RNA greater or less than 2 x 10^6 copies/mL, and HCV genotype (genotype 1 or other).

6.2 Description of Study Population

6.2.1 Baseline Demographic Characteristics

The baseline demographic characteristics of patients enrolled in this study are summarized in the following table.

categories are 4, since it appears that activity in this category best correlates with severity of disease. In grading category 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. Again there are no numerical scores of 7 to 9 given to this category. According to the authors of the HAI score, the composite score can be broken into individual components of necrosis (categories I, II), inflammation (category III), and fibrosis (category IV) for additional evaluation of the disease. (See Appendix A).

Table 2. Baseline Demographic Characteristics

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Age (years):		
- Mean	42.6	44.5
- Range	29-67	28-66
Gender:		
- Male	49 (64%)	53 (70%)
- Female	28 (36%)	23 (30%)
Race:		
- White	71 (92%)	69 (91%)
- Asian	1 (1%)	1 (1%)
- Black	1 (1%)	1 (1%)
- Hispanic	3 (4%)	5 (7%)
- Other	1 (1%)	-

Source: NDA 20-903, Protocol No. C95-145, Vols. 3.45, 3 .50 and 3.51.

Comment: The baseline demographic characteristics of study patients were similar between the two treatment groups.

6.2.2 Baseline Disease Characteristics

The baseline disease characteristics of study participants are presented in Table 3.

Table 3. Baseline Disease Characteristics

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Source of Exposure:		
Transfusion	18 (23%)	21 (28%)
Parenteral	37 (48%)	43 (57%)
Sporadic/Other/Unknown	22 (29%)	12 (16%)
Years Since Exposure:		
Mean[1]	15	18.4
Range		
HCV Genotype		
1 (total)	46 (60%)	42 (55%)
- 1a	21	13
- 1b	16	24
2 (total)	16 (21%)	17 (22%)
- 2a	3	1
- 2b	13	16
3a	15 (19%)	17 (22%)
4h	-	1 (1%)
HCV-RNA[2]		
$\leq 2 \times 10^6$ copies/mL	9 (12%)	12 (16%)
$>2 \times 10^6$ copies/mL	68 (88%)	64 (84%)
Mean	6.5×10^6	6.3×10^6
Knodell HAI score:		
Mean total score (I+II+III)	6.8	6.9
Mean fibrosis score (IV)	1.31	1.5
ALT (upper limit of normal):		
Mean	3.4	3.3
Range		

Source: NDA 20-903, Study C95-144, Volume 3.45, and Appendix 12, Volumes 3.50 and 3.51.
1. Years since exposure was missing for 8 INTRON A + ribavirin and 9 INTRON A + placebo patients.
2. One INTRON A + ribavirin patient entered the study with a baseline HCV-RNA below LOQ of the assay.

Comments: The baseline disease characteristics of the study population were well-balanced between the treatment groups. The mean duration of disease in the study population was slightly higher in the INTRON A + ribavirin arm compared to the INTRON A + placebo arm; 15 years compared to 18.4 years, respectively. However, the baseline Knodell HAI scores (mean: 6.85, range: 2 to 12) reflected relatively mild histological disease in both treatment groups. Baseline fibrosis was also very low in study patients. Only three patients entered the study with evidence of cirrhosis on their baseline liver biopsy and all three were randomized to receive INTRON A + placebo. The mean viral load presented in the table was higher than what was reported by the applicant because the applicant relied on a geometric mean and FDA used a true mean.

6.3 Evaluation Criteria

The applicant's primary endpoint was an overall response rate defined as serum HCV-RNA below the limit of quantification (LOQ) of the assay at 24 weeks of follow-up and improvement of liver biopsy by ≥ 2 points in the Knodell "inflammation" score (defined as the sum of category I, II and III scores) at week 48 (end of follow-up).

The applicant also defined patients with HCV-RNA below the LOQ at any time during the study as "responders." Patients with HCV-RNA below LOQ at 24 weeks of follow-up were classified as "sustained responders." Patients were classified as "non-responders" if the above criteria were not met or if they discontinued the study before the required HCV-RNA measurements were obtained.

Comment: The original protocol-specified definition of a sustained virologic responder was a virologic response at the end of treatment (week 24) maintained to the end of follow-up (week 48). During the conduct of the study, a protocol amendment issued by the applicant that revised the definition of sustained virologic response to be based on a virologic response the end of follow-up, i.e., only at week 48. This change in definition could have allowed patients who had detectable levels of HCV-RNA up to the last study visit to be considered sustained responders, and could have overestimated the true response rate. Therefore, the FDA used the original protocol-specified definition in the analyses of the data in this NDA.

Secondary endpoints included: (1) HCV-RNA responses at week 24 (end of treatment) and at week 48 (end of follow-up), (2) proportion of patients with normalization of ALT at weeks 24 and 48, (3) proportion of patients with overall improvement of liver biopsy findings (based on inflammation scores), and, (4) changes from baseline of liver biopsy scores.

Comments: The "inflammation" score, as defined by the applicant, reflected the sum of category I (periportal +/- bridging necrosis), II (intralobular degeneration and focal necrosis), and III (portal inflammation) scores. This "inflammation" score did not include category IV, i.e., the degree of fibrosis, which is a significant pathological feature of chronic HCV infection. The choice of a 2 point change in histology as a marker of improvement was arbitrary, and the clinical relevance of this magnitude of change has not been established.

6.4 Study Withdrawals and Compliance

Overall, 82% of patients completed the study; 79% in the INTRON A + ribavirin group and 85.5% in the INTRON A + placebo group. Ten INTRON A + ribavirin and five of INTRON A + placebo recipients did not completed the 24 week treatment period. The primary reason for discontinuation during this period was adverse events, seven and three in the INTRON A + ribavirin and INTRON A + placebo groups,

respectively. The remaining patients who discontinued during the treatment period did so because they did not wish to continue (n=4) or due to noncompliance (n=1).

An additional four INTRON A + placebo patients completed 24 weeks of therapy but did not wish to enter the follow-up phase (n=3) or were lost-to-follow-up (n=1). In the INTRON A + ribavirin group, three patients completed the dosing period but either did not wish to continue with the follow-up period, were lost-to-follow-up or were non-compliant.

6.5 Protocol Violations

There were 33 cases of protocol violations with respect to entry inclusion/exclusion criteria. These cases are summarized in Table 4.

Table 4. Entry Criteria Protocol Violations

	INTRON A + Ribavirin	INTRON A + Placebo
Prior interferon <20 or >78 wks	1	1
Improper liver biopsy timing	2	3
Missing baseline liver biopsy	2	1
Indirect bilirubin >0.8 mg/dL	4	5
Fasting glucose >125 mg/dL	1	2
Neutrophils $\leq$1500/mm^3	1	2
Normal ALT (at baseline)		1
TSH <0.2 or >5.5	2	3
HCV-RNA <LOQ	1	
Misrandomized		1

Source: NDA 20-903, General Correspondence dated January 13, 1998, and Volumes 2.45, 2.50 and 2.51.

Comment: One patient in the INTRON A + ribavirin arm had a screening viral load value of 130,000 copies/mL. At the time of randomization, the patient's viral load was <100 copies/mL. Although it was unlikely that this patient had a virologic response to therapy, he was nonetheless included in all of the efficacy analyses. Otherwise, the entry inclusion/exclusion criteria violations did not appear to have compromised patient eligibility, safety, or had a significant impact on study treatment.

6.6 Efficacy Analysis

6.6.1 Virologic Response

The proportion of patients with HCV-RNA below the LOQ at each evaluation time point during the treatment period (weeks 4, 12, and 24) and during follow-up (weeks 36 and 48) are summarized in Table 5.

Table 5. Virologic Responses at Measured Time Points

	Treatment Period			Follow-Up Period	
	Week 4	Week 12	Week 24	Week 36	Week 48
INTRON A + Ribavirin (n=77)	31%	72%	71%	45%	43%
INTRON A + Placebo (n=76)	6.5%	29%	45%	5.2%	3.9%

The proportion of patients with sustained virologic response are presented in the following table.

Table 6. Time to Sustained Virologic Response

	INTRON A + Ribavirin	INTRON A + Placebo
Sustained response	43% (33/77)	4% (3/76)
Non-sustained response/missing	57% (44/77)	96% (73/76)
Time to sustained response		
-By week 4	54.5% (18/33)	100% (3/3)
-By week 12	100% (33/33)	-

Comment: Significantly more patients treated with the combination achieved a virologic response during therapy and maintained that response during the off-therapy follow-up period. In both treatment groups, all of the patients who were sustained virologic responders had achieved their initial virologic response by week 12.

The end-of-treatment response rate (45%) in the INTRON A + placebo arm was comparable to the results of other INTRON A monotherapy studies (approximately 30-40%); however, the six-month post-treatment response rate was significantly lower that has previously been reported, 4% versus 10-20%. The mean baseline level of virus of sustained responders were approximately 6.4 and 2.3 x 10^6 copies/mL for the INTRON A + ribavirin and INTRON A + placebo groups, respectively.

The applicant stratified patients by baseline level of virus ($\leq$ and >2 million copies/mL). Analysis of virologic response based on this cut-off demonstrated that patients with $\leq$2 million copies/mL had a generally more favorable response to therapy than patients with higher baseline levels.

Comment: Baseline viral load was weakly correlated with sustained virologic response. Although the number of patients who entered the study with a baseline viral load of $\leq$2 million copes/mL was small, the results were consistent with reports that patients with lower baseline viral load levels tend to respond more favorably to therapy.

Genotypes 1, 2, and 3 are the most common HCV subtypes in patients from Europe and the United States. Genotypes 1a and 1b have been associated with poor interferon treatment response in previous studies. Among patients in INTRON A + ribavirin group, 28% (13/46) with genotype 1, 75% (12/16) with genotype 2 and 53% (8/15) with genotype 3 had sustained virologic responses. Among virologic non-responders, 71% (33/46), 25% (4/16) and 47% (7/15) had genotypes 1,2 or 3, respectively.

Of the three sustained virologic responders who received INTRON A + placebo, 2% (1/42) had genotype 1 and 12% (2/17) had genotype 3. Ninety-eight percent (41/42), 100% (17/17), 88% (15/17) and 100% (1/1) of virologic non-responders had genotypes 1, 2, 3, or 4, respectively.

Comment: Patient with genotype 1 virus had less favorable virologic response rates than patients with non-genotype 1 virus. The sustained response rate in INTRON A + ribavirin patients with genotype 1 virus was higher, 28%, compared to 2% in the INTRON A + placebo group. Thus, although patients with genotype 1 tend to respond less favorably than patients with non-genotype 1 virus, there did appear to be some benefit conveyed by the combination treatment.

6.6.2 Histologic Response

Complete sets of pre-treatment and end of follow-up biopsies were available for 62/77 (81%) and 64/76 (84%) of INTRON A + ribavirin and INTRON A + placebo patients, respectively. Table 7 presents histologic improvement rates for those patients with paired biopsy data.

Table 7. Histologic Response Rates

	INTRON A + Ribavirin n=61	INTRON A + Placebo n=64
Knodell I+II+III		
-Improvement	62%	42%
-No improvement/worse	38%	58%
Knodell I+II+III+IV		
-Improvement	60%	42%
-No improvement/worse	40%	58%

The overall mean histologic improvements in components I+II+III of the Knodell HAI score were 2.4 points and 0.7 points for patients in the INTRON A + ribavirin and INTRON A + placebo groups, respectively. When component IV (fibrosis) was included, the mean improvement remained 2.4 point and 0.6 points for the INTRON A + ribavirin and INTRON A + placebo groups, respectively.

Among sustained virologic responders the mean histologic improvement was 4.3 points (n=3) for the INTRON A + placebo-treated patients compared to 4.1 points (n=32) for INTRON A + ribavirin-treated patients. Improvement in HAI scores for virologic non-responders was $\leq$ 1 point in both treatment groups. Histologic improvements were primarily observed in components I, II, and III. The fibrosis score (component IV) did not show significant variations.

Comment: The number and reasons for missing end of follow-up biopsies were evenly distributed across the treatment arms and primarily reflected patient refusal to undergo a follow-up biopsy. Although component IV (fibrosis) is an important marker of disease status, its inclusion in the calculation of histologic change did not appreciably affect the results.

6.6.3 Overall Response

The applicant constructed a "maximum likelihood estimate" (MLE) so that patients whose overall response status could not be determined, i.e., patients with missing data, could contribute to the analysis. Using this procedure, the applicant determined that 36.5% of patients treated with INTRON A + ribavirin and 2.7% of patients treated with INTRON A + placebo successfully met the definition of the primary efficacy endpoint. The applicant also conducted an analysis that treated patients with either missing virologic or histologic data as treatment failures. This analysis demonstrated an overall response rate of 32.5% (25/77) and 2.6% (2/76) for the INTRON A + ribavirin and INTRON A + placebo arms, respectively.

Table 8 presents the results of FDA's analyses. Again, an overall response was defined as a sustained virologic response combined with a $\geq$ 2 point improvement in components I+II+III of the HAI score on the post treatment liver biopsy compared to the pre-treatment biopsy. Patients missing either the end-of-follow-up HCV-RNA measurement or who did not have a matched pre- and post-treatment liver biopsy data, or both, were categorized as "missing data" and no assumptions were made about whether they achieved or did not achieve an overall response to therapy.

Table 8. Overall Response Rates

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Virologic Response		
-Sustained response	33	3
-Non-sustained response	36	64
-Missing data	8	9
Histologic Response		
-Improvement	38	27
-No improvement	23	37
-Missing data	16	12
Overall Response	24	2

The inclusion of component IV (fibrosis) in the calculation of histological response affected one patient in the INTRON A + ribavirin arm of the study. By adding component IV, the magnitude of improvement in this patient's total HAI score was reduced from a 2 point improvement to a 0 point change, and would have lowered the overall response rate slightly to 30% (23/77).

Comment: The applicant's and FDA's analyses yielded similar overall response rates and both analyses demonstrated an overall response in favor of the INTRON A + ribavirin combination. The overall response rates were significantly lower that what would be predicted by using either HCV-RNA or histology alone. There were no significant differences in outcomes for males compared to females.

6.6.4 Biochemical Response

ALT response rates at the end of therapy and at the end of follow-up were secondary endpoint measures. The results of this analysis, in addition to the proportion of patients who achieved a normal ALT at the end of therapy and maintained that normalization through the follow-up period are presented in Table 9.

Table 9. ALT Response Rates

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Normal at week 24	57 (74%)	37 (49%)
Normal at week 48	35 (45%)	11 (14%)
Normal at week 24 sustained through week 48	27 (35%)	3 (4%)

Of the 33 sustained virologic responders in the INTRON A + ribavirin arm, 24 (72%) also had sustained normalization of their ALT. Conversely, of the 38 patients who had improvement in histology, only 16 (42%) had normalization of their ALT levels.

Normalized ALT by week 4 was associated with a 56% likelihood of sustained virologic response. If normalization occurred at week 12, the likelihood of a sustained virologic response decreased to 32%. The likelihood of a sustained virologic response decrease to 20% if ALT normalization occurred at the week 24 measurement. A combined virologic response and ALT normalization by week 12 of therapy was associated with a 78% probability of sustained virologic response.

There was general agreement between histologic improvement and ALT normalization at week 48. Twenty seven of the 35 patients in the combination arm with normal ALT levels at week 48 also had improvement in liver histology.

Comment: There was a significantly higher ALT normalization rate in the INTRON A + ribavirin-treated patients compared to those treated with INTRON A + placebo. Although ALT levels were more variable throughout the study period, there was high concordance between a sustained virologic response and normalization of ALT at week 48. Although, there was general concordance between normalization of ALT and improvements in liver histology, normalization of ALT levels underestimated improvements in histology.

6.6.5 Comparison of Responders and Non-Responders

A comparison of the characteristics of responders to INTRON A + ribavirin therapy compared to non-responders is provided in the following table.

Table 10. Comparison of Responders and Non-Responders

Parameter	Overall Responders n=24	Non-Responders n=53
Age (years):		
Mean	40.2	43.8
Range	31 - 57	29 - 67
Gender:		
Male	13 (54%)	37 (72%)
Female	11 (46%)	15 (28%)
Source of exposure:		
Parenteral	13 (54%)	23 (45%)
Transfusion	4 (17%)	14 (26%)
Sporadic/Other/Unknown	7 (29%)	15 (28%)
Years since exposure:		
Mean	14.4	15.0
Range		
HCV Genotype:		
1	7 (29%)	39 (74%)
2	9 (38%)	7 (13%)
3a	8 (33%)	7 (13%)
Baseline HCV-RNA:		
Mean	6.6×10^6	7.1×10^6
Range		
HCV-RNA		
≤ 2 million copies/mL	4	4
>2 million copies/mL	20	47
Mean baseline Knodell[1]	8.33	7.83
Mean baseline ALT (xULN)	5.45	0.54

1. Non-responder category based on 37 patients with matched sets of pre- and post-study biopsies.

Comment: Although there were more males than females enrolled in the study, females had a slightly better overall responses to therapy. Patients with Genotype 1 responded less often than patients with other genotypes. A baseline viral load of ≤ 2 million copies/mL appeared to have a weak association with overall response (p=0.25), but, as noted above, the number of patients with this baseline HCV-RNA level was small. In general, it appears that neither baseline viral load, baseline ALT levels or baseline HAI scores were good predictors of response.

6.7 Safety Analysis

All patients in this study were included in the analysis of safety.

6.7.1 Deaths

There were no deaths reported during this study

6.7.2 Dose Modifications Due to Adverse Events

At some time during the 24-week dosing period, 34% (27/77) of INTRON A + ribavirin-treated patients underwent a dose modification (reduction, interruption, or both) because of an adverse event compared to 17% (13/76) in the INTRON A + placebo group.

Table 11. Dose Modifications Due to Adverse Events

	INTRON A + Ribavirin	INTRON A + Placebo
Neutropenia	4	3
Anemia	6	
GI disorders	3	1
Musculoskeletal pain	3	1
Hyperthyroidism	3	
Dyspnea	2	
Psychiatric-related events	2	1
Elevated bilirubin	1	
Edema	1	
Flu-like symptoms		1
Malaise		1

Eight INTRON A + ribavirin patients subsequently discontinued the study because of the adverse event that caused their dose modification. In the INTRON A + placebo group, only one patient with back pain subsequently discontinued from the study due to the pain (See section 6.7.4).

Comment: The reasons for dose modifications were associated with known complications of INTRON A and ribavirin therapy.

6.7.3 Serious Adverse Events

A total of nine patients, five in the INTRON A + ribavirin arm and four in the INTRON A + placebo arm, had a serious adverse event during the study. The events in the INTRON A + ribavirin arm included: two injuries, one Bell's palsy, one hyperthyroidism and one suicide attempt. One case each of pyelonephritis, back injury, dehydration, and headache occurred in the INTRON A + placebo arm.

6.7.4 Adverse Events Associated with Premature Study Discontinuation

Ten patients discontinued the study, seven in the INTRON A + ribavirin group and three in the INTRON A + placebo group. The events leading to study discontinuation in the INTRON A + ribavirin group included one case of hyperthyroidism, two cases of depression with one suicide attempt, two cases of neutropenia, one case of arthralgias, and one case of arthralgias and emotional lability (mood swings). Nausea, vomiting and dehydration in two patients with pre-existing gastrointestinal disease and worsening musculoskeletal pain in one patient accounted for the three study drug discontinuations in the INTRON A + placebo arm.

Comment: The events leading to study discontinuation were consistent with the types of events associated with INTRON A therapy.

6.7.5 Clinically Important Adverse Events

Chest Pain

Chest pain alone, with palpitations or with tachycardia, was reported in 11 patients, six (8%) and five (6.5%) in the INTRON A + ribavirin and INTRON A + placebo arms, respectively. Four of the patients in the INTRON A + ribavirin arm had a concomitant reduction in their hemoglobin levels ranging from 1.9 g/dL to 4.1 g/dL. Three of the five INTRON A + placebo patients had decreases in their hemoglobin ranging from 0.7 g/dL to 1.7 g/dL. No patients underwent a dose modification or reduction because of a cardiac-related event.

Comment: Cardiac-related events associated with the use of INTRON A + ribavirin may not generalize to populations that include patients with pre-existing severe cardiac disease.

Dyspnea

Dyspnea was reported in 17% (13/77) INTRON A + ribavirin-treated patients and 12% (9/76) in INTRON A + placebo-treated patients. Twelve of the 13 INTRON A + ribavirin patients had concurrent reductions in their hemoglobin levels, with a maximum hemoglobin drops ranging between 1.9 - 5.0 g/dL. Only five patients in the INTRON A + placebo group had a concomitant reduction in hemoglobin from baseline; range 0.3 - 2.8 g/dL.

Two patients in the INTRON A + ribavirin arm had their dose of INTRON A reduced because of dyspnea. Both patients recovered and completed the study.

Comment: Dyspnea associated with anemia was more prevalent in the INTRON A + ribavirin group implying that ribavirin may have increased the severity of this adverse event.

Psychiatric-Related Events

Treatment emergent psychiatric adverse events, including depression, agitation, anxiety, mood swings, emotional lability, and impaired concentration occurred in 47 (61%) INTRON A + ribavirin patients and 36 (47%) INTRON A + placebo patients. As described above three patients in the INTRON A + ribavirin group discontinued the study due to psychiatric-related adverse events.

Treatment-emergent depression occurred in 23% (18/77) and 16% (12/76) of patients in the INTRON A + ribavirin and INTRON A + placebo arms, respectively. Table 12 summarizes the incidence and outcomes of depression that occurred during the 24 weeks of treatment in this trial.

Table 12. Treatment-Emergent Depression

	INTRON A + ribavirin (n=18)	INTRON A + placebo (n=12)
Median time to onset	RX4	RX8
Median time to resolution	FU8	RX24
Received/changed treatment	10	6
Suicide attempts	1	0

Five of the 18 INTRON A + ribavirin patients continued to have depression listed as an adverse event at end of study; three of these patients continued to receive antidepressant therapy as they exited the study. Only one INTRON A + placebo patient continued to have depression at the end of the study, but this patient discontinued antidepressant therapy during follow-up week 12.

The one attempted suicide that occurred in INTRON A + ribavirin group (#24-003) was in a 34 year old female with a history of intravenous drug abuse and alcohol abuse, but no prior history of depression. The patient experienced the onset of treatment emergent depression during treatment week 12 and was treated with Trazadone. Approximately treatment week 20 (day 155) the patient attempted suicide. According to

the applicant, the patient had reported that she had discontinued study medications approximately four weeks prior to the suicide attempt.

Comment: The incidence of treatment-emergent depression in this study was generally consistent with the rates reported in patients with chronic hepatitis C undergoing INTRON A monotherapy, approximately 19%.

Pregnancies

Because ribavirin has been demonstrated to be teratogenic and embryocidal in animal studies, and the interferons are known abortifacients, pregnancies that occurred either in a patient or his/her partner were examined. There were two such pregnancies reported in this study. The first pregnancy occurred in the spouse of a patient who was receiving INTRON A + placebo; the pregnancy resulted in delivery of a healthy full-term baby. The second pregnancy was in the spouse of a patient randomized to INTRON A + ribavirin; the outcome of this pregnancy is currently unknown.

Thyroid-Related Events

In the INTRON A + ribavirin patients, clinically significant elevations of TSH occurred in six patients during the 24 week dosing period. The elevations ranged from a low of 13.3 MIU/L to a high of 114 MIU/L, and generally the highest value for any patient was reported at the end-of-treatment visit. Three of these patients had a history of hypothyroidism at study entry, two of which had been receiving supplemental thyroid therapy. Treatment was initiated or modified in four of the six, and the other two patients did not receive therapy. In all six, TSH levels returned to normal or near-normal by follow-up week 12.

One INTRON A + ribavirin patient (#33-007) discontinued the study due to clinical events associated with hyperthyroidism. This patient entered the study with a TSH of 1.5 MIU/L, which subsequently decreased to 0.07 MIU/L during treatment week 12. During this period the patient complained of tachycardia and palpitations. His study medications were discontinued during treatment week 16.

Clinically significant elevations in TSH levels occurred in two INTRON A + placebo patients; one each to 67 MIU/L and 23.3 MIU/L at the end of treatment week 24 visit. Both patients entered the study with a history of hypothyroidism, both were receiving thyroid-related medications, both had modifications of their thyroid medications during the study, and both had their TSH subsequently return to normal levels by the week 24 end of follow-up visit.

Conversely, decreases in TSH levels below 0.2 MIU/L (lower limit for study inclusion) occurred at some time during the 24-week treatment period in nine INTRON A + ribavirin and three INTRON A + placebo patients, respectively. Two of the INTRON A + placebo patients entered the study with a history of hypothyroidism on synthroid. Neither patient had a change in their thyroid therapy, and both had subsequent normalization of their TSH levels by their next scheduled visit. The third INTRON A + placebo patient had a reduction in his TSH to 0.01 MIU/L at the week 24 visit. The patient did not enter the follow-up period so it is unknown if his hypothyroidism resolved.

Comment: Thyroid dysfunction occurred more frequently in patients with underlying thyroid disease. These events were generally treated by the addition or adjustments of thyroid medications. Only one patient in the INTRON A + ribavirin group discontinued due to tachycardia associated with hyperthyroidism.

6.7.6 Laboratory Abnormalities

Hemoglobin Levels

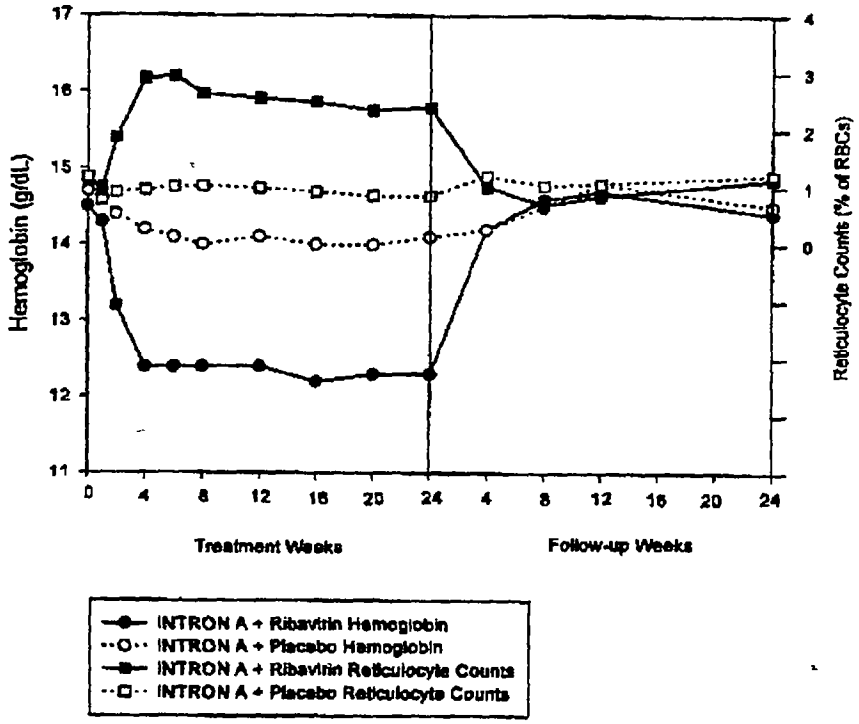
No INTRON A + placebo-treated patients had a reduction in hemoglobin to below 11.5 g/dL, and no patients in this group underwent dose modification.

The mean maximum hemoglobin decrease was 2.8 g/dL in the INTRON A + ribavirin arm compared to <1 g/dL in the INTRON A + placebo arm. Hemoglobin levels began to drop during week 1 and stabilized by week 4.

Overall, 75% (58/77) of INTRON A + ribavirin-treated patients had reductions in hemoglobin ≥2 g/dL from baseline compared to 8% (6/76) in the INTRON A + placebo arm. Nine of the INTRON A + ribavirin patients had a reduction from baseline between 4 and 6 g/dL, eight of which had reductions to below 10 g/dL, the level at which dose modifications were to occur.

Dose reductions of ribavirin for low hemoglobin levels was instituted for six of these patients. Hemoglobin levels returned to pre-treatment levels between 4 to 8 weeks following cessation of ribavirin therapy.

FIGURE 1. MEAN HEMOGLOBIN LEVELS AND RETICULOCYTE COUNTS



Source: NDA 20-903, Volume 3.45, page 113.

Comment: Anemia was very common in the INTRON A + ribavirin group. Anemia occurred in a relatively short period of time (within 1-2 weeks), stabilized by week 4 and generally returned to normal levels within 4-8 weeks following cessation of ribavirin therapy. Anemia may have been temporally associated with chest pain and/or dyspnea in a few patients. (See section 6.7.5).

Platelet Counts

Treatment with INTRON A + ribavirin had little effect on platelet counts. The mean baseline platelet counts were the same in both treatment groups (202 x 10^9/L). The mean nadir platelet count in the INTRON A + ribavirin group was 164 x 10^9/L compared to 144 x 10^9/L in the INTRON A + placebo group.

Absolute reductions in platelet counts to ≤150,000/mm^3 occurred in four (5%) INTRON A + ribavirin patients and 13 (17%) INTRON A + placebo patients during the 24 week treatment period. No patient in this study had a dose modification, reduction, or discontinued study medication due to a decrease in platelet count.

Comment: Ribavirin treatment did not appear to influence the incidence of thrombocytopenia in study patients.

White Blood Cell counts

The mean WBC count was slightly lower in the INTRON A + ribavirin arm at week 4 compared to the INTRON A + placebo arm, 4.1 versus 4.6 x 10^9/L, respectively. Most of the WBC counts returned to normal levels within 4 weeks following cessation of therapy.

The mean baseline absolute neutrophil count (ANC) were similar between the treatment groups, 3.2 x 10^9/L in the INTRON A + ribavirin arm and 3.5 x 10^9/L in the INTRON A + placebo arm. The mean maximum ANC reductions during the treatment period were 1.9 x 10^9/L and 2.1 x 10^9/L in the INTRON A + ribavirin and INTRON A + placebo arms, respectively.

Thirteen INTRON A + ribavirin patients had reductions in their neutrophil counts to < 750/mm^3 during the treatment period. Four patients underwent a dose modification of ribavirin or INTRON A, or both, with subsequent recovery of their ANC; seven had no change in their study medications; and, two discontinued the study due to neutropenia. In the INTRON A + placebo group, 11 patients had reductions in ANC below 750/mm^3; only three underwent dose modifications. No INTRON A + placebo-treated patients discontinued therapy due to neutropenia.

Further, neutropenia was associated with infection in three INTRON A + placebo-treated patients (pharyngitis n=3 and chest congestion n=1), and on INTRON A + ribavirin-treated patient (pharyngitis).

Comment: The addition of ribavirin did not appear to potentiate the neutropenic effects of INTRON A.

6.7.7 All Adverse Events

Adverse events were reported by 100% of INTRON A + ribavirin and 99% of INTRON A + placebo patients during the 24-week dosing period. The most commonly occurring adverse events are presented in the following table.

Table 13. Selected Treatment Emergent Adverse Events (all grades)

Adverse Event	INTRON A + Ribavirin n (%)	INTRON A + Placebo n (%)
Asthenia	8 (10)	3 (4)
Chest pain	5 (6)	5 (7)
Edema	3 (4)	3 (4)
Fatigue	46 (60)	40 (53)
Fever	25 (32)	27 (36)
Headache	51 (66)	52 (68)
Rigors	33 (43)	28 (37)
Dizziness	20 (26)	16 (21)
Abdominal pain	13 (17)	19 (25)
Anorexia	16 (21)	11 (14)
Diarrhea	13 (17)	19 (25)
Dyspepsia	12 (16)	7 (9)
Nausea	36 (47)	25 (33)
Vomiting	9 (12)	6 (8)
Arthralgia	22 (29)	22 (29)
Musculo-skeletal pain	17 (22)	21 (28)
Myalgia	47 (61)	44 (58)
Anxiety	7 (9)	7 (9)
Concentration impaired	8 (10)	9 (12)
Depression	18 (23)	12 (16)
Emotional lability	9 (12)	6 (8)
Insomnia	20 (26)	19 (25)
Irritability	19 (25)	15 (20)
Infection-viral	10 (13)	8 (11)
Pruritis	10 (13)	3 (4)
Alopecia	21 (27)	20 (26)
Rash	16 (21)	4 (5)
Dyspnea	13 (17)	9 (12)
Flu-like symptoms	10 (13)	10 (13)

Source: NDA 20-903, Volume 3.45

Comment: Depression, pruritis, nausea, and rash occurred somewhat more frequently in the INTRON A + ribavirin treatment arm. There were three cases of neutropenia, two in the INTRON A + ribavirin arm and one in the INTRON A + placebo arm that were considered "life-threatening." There were no gender differences in types or frequencies of adverse events noted.

6.8 Assessment of Safety and Efficacy Based on Study C95-144

6.8.1 Efficacy

Evidence of efficacy was supported by greater virologic and histologic responses in INTRON A + ribavirin combination compared to those treated with INTRON A + placebo.

Seventy-five percent of INTRON A + ribavirin-treated patients compared to 45% of INTRON A + placebo-treated patients achieved a virologic response by the end of treatment; however, only 43% and 4% sustained the response throughout the follow-up period. All of the patients who demonstrated a sustained virologic response achieved their initial virologic response by week 12.

Of patients who had complete sets of pre- and post-study liver biopsies, histologic improvement in the INTRON A + ribavirin group was greater than in the INTRON A + placebo-treated group 62% compared to 38%, respectively. The inclusion of component IV (fibrosis) in the analysis of histology did not impact the outcomes in this study. There were too few numbers of patients with cirrhosis at baseline to assess the impact of therapy on this parameter.

Virologic responders had greater improvements in liver histology compared to virologic non-responders.

ALT levels were variable throughout the study. ALT normalization occurred in a significantly higher proportion of patients treated with INTRON A + ribavirin compared to INTRON A + placebo-treated patients. There was a high correlation between an end of follow-up HCV-RNA level below LOQ and normal ALT levels. Patients with both a virologic response and normalization of ALT by week 4, or virologic response by week 4 alone, had a higher probability of a sustained virologic response than those who only achieved an ALT response at week 4. Finally, normal ALT levels at week 48 were generally associated with improvements in liver histology.

Patients with non-genotype 1 virus responded better than patients with genotype 1 regardless of treatment received. Patients with baseline viral loads of ≤ 2 million copies/mL appeared to have a more favorable response than patients with higher baseline levels. However, there were very few patients with baseline levels below 2 million to support a treatment decision. When analyzed together, lower baseline viral load and non-genotype 1 were weakly correlated with an improved virologic response to therapy.

This study failed to clearly identify a specific patient population that were likely to have a high response to therapy. In general, male patients and patients with Genotype 1 generally had less favorable responses to therapy. Baseline viral load, baseline HAI score and baseline line ALT levels were not predictive of a response to therapy.

To conclude, the results of this study demonstrated a short-term benefit for patients treated with the combination compared to those re-treated with interferon monotherapy. In general, sustained virologic response was associated with normalization of ALT levels and improvements in liver histology.

6.8.2 Safety

No deaths occurred in this study. Similar numbers of patients in both treatment groups required dose modifications because of neutropenia and psychiatric-related events. Dose modifications due to anemia (reductions in hemoglobin) occurred only in the INTRON A + ribavirin group.

More patients in the INTRON A + ribavirin group experienced serious and life-threatening adverse events including neutropenia, depression, including one attempted suicide, and thyroid dysfunctions than the INTRON A + placebo group.

Patients with significant underlying psychiatric disorders at baseline were excluded from the study. Overall, 62% of study participants experienced a psychiatric-related event; irritability, depression and insomnia being the most common events. The incidence of treatment-emergent depression in this study was common but generally consistent with the incidence of depression reported in previous studies of INTRON A. One patient in the INTRON A + ribavirin group who became depressed on therapy attempted suicide.

Ribavirin induced anemia occurred in the majority of patients, with over 70% of combination treated patients having a ≥2 g/dL reduction from baseline. The onset of anemia was rapid, within the first 1-2 weeks of therapy. Anemia was generally reversible following cessation of treatment. Increased rates of chest pain and dyspnea occurred in some patients treated with the combination, and in some cases these events were associated with reductions in hemoglobin levels. Patients with severe pre-existing cardiovascular disease were excluded from entry into this study.

Neutropenia was also a common hematological adverse event, occurring in similar numbers of patients in both treatment groups. However, more patients in the INTRON A + ribavirin group underwent a dose modification or discontinued therapy due to neutropenia. A higher proportion of patients in the INTRON A + placebo group had reductions in their platelet counts.

Other reported adverse events were very common in both treatment groups, the majority of which were of mild to moderate severity. Overall, the adverse events seen in this study were similar to those associated with the use of INTRON A. There was no apparent differences in the types or frequency of adverse events seen in females compared to males. With the exception of anemia, it did not appear that the addition of ribavirin potentiated the laboratory abnormalities seen in this study.

The types of adverse events in this study were consistent with the known safety profiles of INTRON A and ribavirin; however, they were reported more frequently in the combination arm. The primary toxicities of concern included anemia and depression.

7.0 Clinical Trial I95-145

"Interferon Alfa-2B (INTRON A) monotherapy versus Interferon Alfa-2B (INTRON A) + Ribavirin (Sch 18908) for treatment of relapse in patients with chronic hepatitis C."

This was a second phase III, prospective, randomized, double-blinded study of 192 HCV infected patients designed to compare the safety and efficacy of the combination of INTRON A + ribavirin to INTRON A + placebo. The study inclusion/exclusion criteria, dosing regimens, evaluation criteria were the same as in study C95-144.

The efficacy analyses demonstrated that the responses to therapy were similar in both treatment groups to those seen in study C95-144. The types of adverse events were also similar between the two studies. Of note, however, the reported frequency of events were generally lower in this trial. The lower reporting appears to be consistent with a general lower reporting by non-US investigators.

For a comprehensive review of study I95-145, please see the review by Dr. Tan Nguyen that is appended to this review (See Appendix B).

8.0 Supportive Safety Data

In addition to complete safety data from the two phase 3 trials, the applicant has submitted the following: (1) interim blinded safety data from approximately 1744 patients currently enrolled in two ongoing double-blind, randomized trials of INTRON A + placebo or ribavirin in patients naïve to INTRON A; (2) serious adverse events and deaths that have occurred during other Schering-sponsored and investigator-initiated studies; and, (3) serious adverse events and deaths that have occurred during open-label and expanded use. A review of these data are presented below.

8.1 Clinical Trials C95-132 and I95-143

The applicant has provided blinded safety data from two ongoing trials that compare combination therapy of INTRON A + ribavirin with INTRON A + placebo in patients who have not previously received INTRON A. Patients in these trials were randomly assigned to receive Intron A 3 MIU TIW plus ribavirin

1000 or 1200 mg/day (n=1010) or Intron A 3 MIU TIW plus placebo (n=734) for either 24 or 48 (n=915) weeks followed by a 24 week off therapy follow-up period. The reporting period for these studies is August 1, 1995 though January 28, 1998.

8.1.1 Deaths

Five deaths have occurred in the two naïve studies.

Two deaths due to myocardial infarctions occurred during the first 24 weeks of study C95-132. The first death (patient #15-039) occurred in a 56 year old black male with a history of diabetes, angina, hypertension and previous myocardial infarction. Four weeks prior to death the patient had a 6 g/dL reduction from baseline in his hemoglobin to 9.6 g/dL. The dose of ribavirin was reduced but his hemoglobin remained low (between 10.3 g/dL and 9.3 g/dL). The patient had an acute myocardial infarction and died during treatment week 20.

The second cardiac-related death (patient #39-012) occurred during treatment in a 59 year old caucasian male with a history of hypertension and diabetes. Approximately treatment week 20, the patient had an acute inferior wall and right ventricular myocardial infarction. Cardiac catheterization revealed triple vessel disease. The patient underwent coronary artery bypass surgery, but died during surgery. This patient had a reduction from baseline in hemoglobin from 16.5 g/dL to 13.2 g/dL at the time of death. This patient was receiving INTRON A + placebo.

Two deaths due to illicit drug overdoses occurred in study C95-132. The first death (patient #35-002) occurred during follow-up week 16 in a 43 year old male patient with a history of illicit drug use and depression. This patient had successfully completed 48 weeks of blinded study medication. The other drug overdose occurred in patient #44-019. This patient was a 43 year old female with a history of mild depression who died of an "accidental" overdose while in her 36th week of receiving blinded study medication.

The one death in study I95-143 (patient #25-005) occurred during follow-up week 20 and was due to an intracranial hemorrhage secondary to a fall.

Comment: Both deaths due to myocardial infarctions occurred in patients with pre-existing cardiovascular disease and diabetes. Both deaths due to drug overdoses occurred in patients with pre-existing depression. These deaths were possibly associated with study medication. The death due to intracranial hemorrhage was not attributable to study medication.

8.1.2 Serious Adverse Events

A total of 202 patients reported 370 serious adverse events during the treatment or follow-up period. The most commonly reported events included: hepatic neoplasms (2), chest pain (10), myocardial infarction (6), angina (3), hypertension (2), fever (12), anemia (2), thyroid dysfunction (16), abdominal pain (17), vomiting (13), pneumonia (5), depression (5), hallucinations (4), anxiety (4), suicidal ideation (6), suicide attempt (8), aggressive reaction (5), and dyspnea (6).

Comment: The types of serious adverse events listed herein are, again, consistent with the adverse event profiles seen with the use of INTRON A and ribavirin in the relapse studies reviewed above. The events remain blinded to study treatment.

8.1.3 Withdrawals for Adverse Events

According to the applicant, 137 (8%) patients discontinued the study during the first 24 weeks of dosing because of an adverse event. A total of 109 discontinued study medication due to a psychiatric-related event, including: depression (26), suicidal ideation (7), suicide attempt (2), anxiety (5), emotional lability (3), aggressive behavior (2), insomnia (1), irritability (4), abnormal thinking (1), impaired concentration (1), neurosis (1), agitation (1) or hallucinations (1).

There were eight patients who discontinued study medication due to a cardiac-related adverse event, i.e., chest pain/angina, myocardial infarction or cardiac failure.

Comment: The treatment arms remain blinded. Serious cardiac-related events and serious psychiatric-related events (anxiety, depression, suicidal ideation and attempts) were the most common reason for study drug discontinuation. These reasons are consistent with the reasons for discontinuation seen in the relapse studies reviewed above.

8.1.4 Pregnancies

Nineteen pregnancies have been reported between the two naïve patient trials; seven in patients and 12 in partners. The outcomes of these pregnancies include: miscarriage (9), voluntary termination (3), delivery of a healthy baby (2), and unknown (5). The treatment groups for many of these cases remains blinded.

8.1.5 All Adverse Events

Adverse events were reported by 98% of INTRON A + ribavirin and 99% of INTRON A + placebo patients during the first 24 weeks of the study. The most commonly occurring adverse events are presented in the following table.

Table 14. Selected Treatment Emergent Adverse Events (all grades)

Event	INTRON A + Ribavirin n (%)	INTRON A + Placebo n (%)
Application site disorders	122 (12)	120 (16)
Asthenia	195 (19)	102 (14)
Chest pain	39 (4)	28 (4)
Fatigue	528 (52)	405 (55)
Fever	336 (33)	255 (35)
Headache	579 (57)	439 (60)
Rigors	276 (27)	199 (27)
Dizziness	133 (13)	92 (13)
Abdominal pain	123 (12)	113 (15)
Anorexia	211 (21)	115 (16)
Diarrhea	153 (15)	141 (19)
Dyspepsia	95 (9)	46 (6)
Nausea	315 (31)	195 (27)
Vomiting	76 (8)	63 (9)
Arthralgia	233 (23)	197 (27)
Musculoskeletal pain	207 (20)	172 (23)
Myalgia	460 (46)	369 (50)
Anxiety	93 (9)	61 (8)
Concentration impaired	87 (9)	73 (10)
Depression	234 (23)	160 (22)
Emotional lability	64 (6)	40 (5)
Insomnia	312 (31)	166 (23)
Irritability	184 (18)	119 (16)
Infection-viral	104 (10)	79 (11)
Pruritis	186 (18)	50 (7)
Alopecia	242 (24)	184 (25)
Rash	157 (16)	48 (7)
Dyspnea	142 (14)	53 (7)
Flu-like symptoms	250 (25)	184 (25)
Anemia	75 (7)	1 (<1)

Source: NDA 20-903, Volume 3.75, Attachment 10 and 11

Comment: Overall, the types and frequency of adverse events were similar to those reported in the relapse studies reviewed above.

8.2 Treatment Protocols/Investigator-Initiated Studies/Open-Label Use

Approximately 25,000 patients have received ribavirin either alone or in combination with interferon in Schering-controlled treatment protocols, investigator-initiated studies, or in worldwide open-label use between August 1, 1995 and January 28, 1998.

8.2.1 Deaths

A total of 17 deaths have been reported in this patient population. Each death is summarized below.

- A suicide occurred in a 51 year old male in a treatment protocol who was receiving re-treatment with INTRON A + ribavirin following a relapse of his HCV after a previous course of interferon monotherapy. The patient experienced anxiety but had not exhibited any overt depressive symptoms.

He committed suicide by drowning himself approximately one month after initiating combination therapy.

- A 56 year old male in a treatment protocol committed suicide approximately 11 months after starting INTRON A + ribavirin. At the time of death, the investigator noted that the patient was exhibiting depressive symptoms. The patient had no previous history of depression.
- A literature report of a 58 year old male who was receiving interferon + ribavirin for relapse of his hepatitis C following orthotopic liver transplantation. The patient was reportedly non-compliant with his medications and died from complications associated with chronic rejection.

- A 34 year old male died suddenly during the screening phase of a treatment protocol. The patient had not yet received either interferon or ribavirin. The cause of death was not able to be determined.

- A 46 year old female died due to purulent meningitis possibly secondary to metastases from hepatocellular carcinoma. The patient was receiving ribavirin monotherapy as part of a treatment protocol at the time of death.

- A 68 year old male received ribavirin monotherapy for 5 months. Approximately four weeks after cessation of ribavirin therapy the patient died of cardiac failure associated with liver failure. This patient had both chronic HCV and cirrhosis.

- A 34 year old male who received open-label INTRON A + ribavirin died of a subarachnoid hemorrhage due to a ruptured congenital aneurysm. The patient had been receiving combination treatment for approximately two months prior to death.

- A 42 year old female died due to variceal hemorrhage and thrombocytopenia (platelet counts not provided). The patient was receiving open-label ribavirin with Roferon at the time of her death.

- A 59 year old male died of cardiac failure secondary to intestinal ischemia. While receiving INTRON A + ribavirin, the patient had episodes of neutropenia (ANC 0.7), feeling "down in the dumps" and hearing voices. The patient was admitted because of fever, chills and a productive cough and pneumonia. The next morning he was found unconscious; resuscitative efforts failed and the patient died.

- A 55 year old male died of renal and liver failure with septic shock secondary to abdominal ischemia. The patient had been off of INTRON A + ribavirin therapy for over one year at the time of his death.

- A 55 year old female with a history of hypertension received therapy with INTRON A + ribavirin under a treatment protocol. Seventeen weeks after initiating therapy the patient complained of shortness of breath, hemoptysis and left-sided pleuritic chest pain. Pulmonary infiltrates were found on chest x-ray. The patient had decompensation of her respiratory status and was placed on a ventilator. She died approximately two weeks later of a pneumonia (type unknown).

- A 59 year old male died of cardiac arrest approximately one month after commencing Roferon and open-label ribavirin. The patient had a history of ischemic cardiomyopathy and had undergone a coronary artery bypass approximately 8 years prior to death.

- A 47 year old male experienced sudden death due to a coronary thrombosis approximately four weeks after cessation of open-label INTRON A + ribavirin therapy. This patient had no prior history of cardiovascular disease.

- A 65 year old male with poorly controlled hypertension initiated open-label Intron A + ribavirin therapy in January 1997. In January 1998, the patient died of a massive cerebral hemorrhage.

- A 20 year old male in a treatment protocol died when his car was hit by another car in an accident.

- A 42 year old male who received INTRON A + ribavirin in a treatment protocol died suddenly approximately one month following discontinuation of therapy. The cause of death was reported to be a methadone overdose.

- A 73 year old female died of a presumed cardiac arrhythmia approximately five moths following cessation of INTRON A + open-label ribavirin therapy.

Comment: Six on-therapy deaths were possibly associated with use of ribavirin and/or interferon: two suicides, one cardiac arrest in a patient with a cardiac history, two pneumonias, and one hemorrhage with concomitant thrombocytopenia.

8.2.2 Serious Adverse Events

Serious psychiatric, hematological and cardiovascular events have been reported in this patient population.

Commonly reported serious psychiatric events included: depression, suicidal ideation, suicide attempts, successful (accomplished) suicides, aggressive reactions, agitation, anxiety, emotional lability, hallucinations, nervousness, paranoid reaction, schizophrenia, psychoses, insomnia, and irritability.

The serious cardiovascular adverse events most often reported were; myocardial infarction, angina, cardiac arrest/failure, palpitations, hypertension, hypotension, arrhythmia, and pericardial effusions. Dyspnea was also a commonly reported serious adverse event.
Hemoglobinemia, granulocytopenia and thrombocytopenia were the most common hematological events reported.

Comment: There were no unexpected serious adverse events reported. Given the mix of controlled and uncontrolled use of ribavirin in this patient population, the incidence rate of any one event or a group of associated events cannot be calculated with confidence.

8.2.3 Pregnancies

Seven pregnancies were reported in patients (4) or their partners (3). Two patients and three partners became pregnant while one of the pair was receiving INTRON A + ribavirin. Two pregnancies ended in miscarriages and the outcomes for the other three are unknown. One patient became pregnant during the screening period for an individual-investigator study and had a voluntary termination. The seventh patient had a miscarriage four weeks after receiving ribavirin in a single-dose pharmacokinetics study.

9.0 Overall Summary of Efficacy and Safety

9.1 Efficacy

The results of two double-blind, randomized, controlled trials were submitted by the applicant in support of the efficacy of INTRON A + ribavirin in the treatment of chronic HCV infection in patients who had relapsed following a response to previous INTRON A therapy. A total of 345 patients were randomized to receive INTRON A + ribavirin or INTRON A + placebo for 24 weeks followed by a 24 week off-therapy follow-up period. Efficacy analyses were based on sustained virological response, improvements in liver histology, and an overall response endpoint that combined both these parameters.

The results of these studies demonstrated that:

- Treatment with the combination resulted in significantly greater sustained virologic responses. There was a trend toward a more favorable virologic response in patients with lower baseline viral loads and

those with non-genotype 1 virus. Finally, patients who did not achieve a virologic response by week 12 of therapy did not achieve a sustained virologic response.

- Although liver biopsies are associated with a certain amount of morbidty, the applicant was very able to obtain complete pre- and post-study biopsy sets in 80% of study participants. Treatment with the combination resulted in higher histologic improvement rates compared to treatment with INTRON A + placebo, 60% and 40%, respectively.

- Overall response rates were also similar across the two studies. In study 144, overall response to therapy was 31% and 2.6% in the INTRON A + ribavirin and INTRON A + placebo groups, respectively. In study 145, the rates were 35% and 4.2%. When the overall response results from both studies are combined, patients treated with INTRON A + ribavirin demonstrated a 10-fold greater response (33%) compared to patients treated with INTRON A + placebo (3%). Further, a sustained virologic response was associated with higher improvements in liver histology.

- ALT levels were more variable throughout the study period. However, patients who had a normal ALT value at week 48 generally also had an HCV-RNA below the LOQ at week 48. There was generally good correlation between normalization of ALT at week 48 and improvements in biopsy scores.

Dose
The regimen of INTRON A used was the licensed regimen at the time the studies were initiated. The dose of ribavirin was based on the maximally tolerated dose identified early in the drug's development and used in previous monotherapy studies. The applicant has not completed any dose ranging studies to determine if other doses of ribavirin might have achieved similar or better response rates.

Duration
The applicant submitted data from six months of therapy with six months of post-therapy follow-up. In both studies, time to initial virologic response was predictive of sustained virological response. Specifically, all of the patients who were sustained virologic responders had achieved their initial response by week 12 of therapy. There are currently no data on the safety or efficacy of shorter or longer treatment regimens of this combination.

Parameters of response
The clinical relevance of small improvements in the inflammatory score components of the Knodell system are unknown given the problems with of sampling inherent in liver biopsy specimens, as well as inter-reader variability. However, it is reasonable to suspect that reduction in hepatic inflammation on biopsy should correlate with reductions in HCV-RNA and lowering of serum ALT indicating improvement in liver injury, but additional data to validate this suspicion are still needed. The choice of a ≥ 2 point change in histology to denote improvement was arbitrary, and the results of these studies may have been significantly different if a greater magnitude of improvement would have been required for success.

Population
Overall, the two clinical trials contained in this NDA provide adequate evidence that a six-month course of treatment with the combination of INTRON A + ribavirin is superior to INTRON A alone in achieving a virologic and histologic response in patients who relapse following a response to previous alfa-interferon therapy. in a healthy population with mid diesease

At best, the results of these studies demonstrate a short-term benefit on three surrogates for response in a selected population of patients with relatively mild and compensated liver disease who had previously responded to interferon monotherapy.. The impact on long-term clinical outcomes, such as progression to cirrhosis, liver failure, transplantation, or death remain to be determined. Further investigations into other populations of HCV-infected patients, e.g., patients with more advanced liver disease or patients who have failed previous interferon therapy, should be undertaken.

9.2 Safety

The safety database for this NDA consists of nearly 30,000 patients from controlled studies (n=2100), or treatment protocols and open-label use (n=25,000).

Deaths, primarily due to psychiatric and cardiovascular-related events, suggest that caution must be used in patients with pre-existing disorders. Cardiovascular-related events in patients with concomitant reductions in hemoglobin levels were reported and accounted for two deaths. Psychiatric related deaths, primarily suicides and illicit drug overdoses in patients with treatment-emergent depression also occurred during treatment with INTRON A + ribavirin. The remaining deaths were generally due to either complications of chronic HCV infection or where unrelated to the disease or treatment.

Adverse events occurred in nearly all of the patients in the two relapse studies. The types of events were consistent with those associated with either interferon or ribavirin therapy. The frequency of events was generally higher in the combination arms of the two studies.

It is well established that the interferons cause a spectrum of CNS dysfunctions ranging from mild irritability and memory impairments, to more severe toxicities such as depression and impaired problem solving, psychoses and delerium. A significant proportion of patients reported a psychiatric-related adverse events in both treatment arms of the two studies. The overall rates of depression reported in the US study were higher than reported in the International study. This difference was most likely accounted for by the general under-reporting of adverse events by non-US investigators. Suicidal behavior, including ideation, attempts and successful suicides, occurred in <1% of all the patients in the safety database. However, it is important to note that patients with significant underlying psychiatric diseases were excluded from study entry. There was no evidence to suggest that ribavirin potentiated the occurrence or severity of these events.

The dose of ribavirin used in the two clinical trials caused a significant amount of anemia in patients treated with INTRON A + ribavirin. Reductions from baseline in hemoglobin levels occurred quickly, within 1-2 weeks of the onset of ribavirin therapy. Hemoglobin levels generally stablized by week 4 and returned to normal in most patients within 4-8 weeks of cessation of therapy. Over 10% of patients treated with the combination had a reduction in hemoglobin to less than 10 g/dL compared to no patients in the INTRON A + placebo groups. Certain cardiovascular-related adverse events, including chest pain and dyspnea, occurred more frequently in patients who also had reductions in hemoglobin levels. More patients who received combination therapy required dose modifications due to anemia. Patients with significant pre-existing cardiovascular disease were excluded from the trials. Therefore, it is not entirely clear how patients with significant underlying cardiovascular disease or decreased cardiac reserve will tolerate this combination. These patients should be monitored closely and therapy should be discontinued in patients who exhibit worsening of their cardiovascular status.

Thrombocytopenia, neutropenia, and thyroid dysfunction are well-established adverse events associated with INTRON A use, and they occurred at frequencies that were not inconsistent with rates previously reported. Again, there was no apparent increase in either incidence or severity of these events were attributable to ribavirin.

Pregnancies occurred in both patients and their partners while receiving ribavirin with or without INTRON A. INTRON A is a known abortifacient and animal data has demonstrated that ribavirin is teratogenic and embryocidal. Women of child bearing potential and their partners receiving treatment with INTRON A + ribavirin will be exposed to both drugs for an extended period of time. Therefore, there should be widespread education of clinicians and patients about avoiding pregnancy during treatment and for six months following cessation of therapy, and there should be careful monitoring of the incidence and outcomes of pregnancies associated with the use of these agents.

10.0 Quality-of-Life

The section of the NDA dedicated to QOL was reviewed by staff in the Division of Drug Marketing, Advertising and Communications. A full report of their findings are included in Appendix C. A summary of the major issues include:

- No information on the development of the specific questions related to QOL in patients with hepatitis was submitted. Without such data, the validity of the instrument could not be substantiated.
- The sponsor failed to pre-specify the QOL endpoints prior to the initiation of the study.
- The sponsor did not specify a minimum meaningful difference for the QOL scales. Therefore, it is unknown if the differences seen were meaningful.

11.0 Labeling

The initial proposed labeling by the applicant was long and provided substantial information drawn from the Intron A label. Negotiations between the agency and the applicant focused on streamlining the label to provide specific information about the combination while retaining important risk information about each individual component of the therapy. A face-to-face meeting between the agency and the applicant occurred on May 5, 1998, at which time general agreement about the format and content of each section of the labeling was agreed upon. The final draft labeling submitted on May , 1998, adequately addressed the concerns raised by the NDA reviewers.

12.0 Phase IV Commitments

In the Phase IV (post-marketing) stage of Rebetol/INTRON A development, the applicant has agreed to the following commitments:

13.0 Recommended Regulatory Action

Based on the information submitted in NDA 20-903, this application for combination therapy of patients with HCV infection with INTRON A + Rebetol who have relapsed following previous interferon monotherapy is approvable.

Russell Fleischer, PA-C, MPH
Regulatory Review Scientist, DAVDP

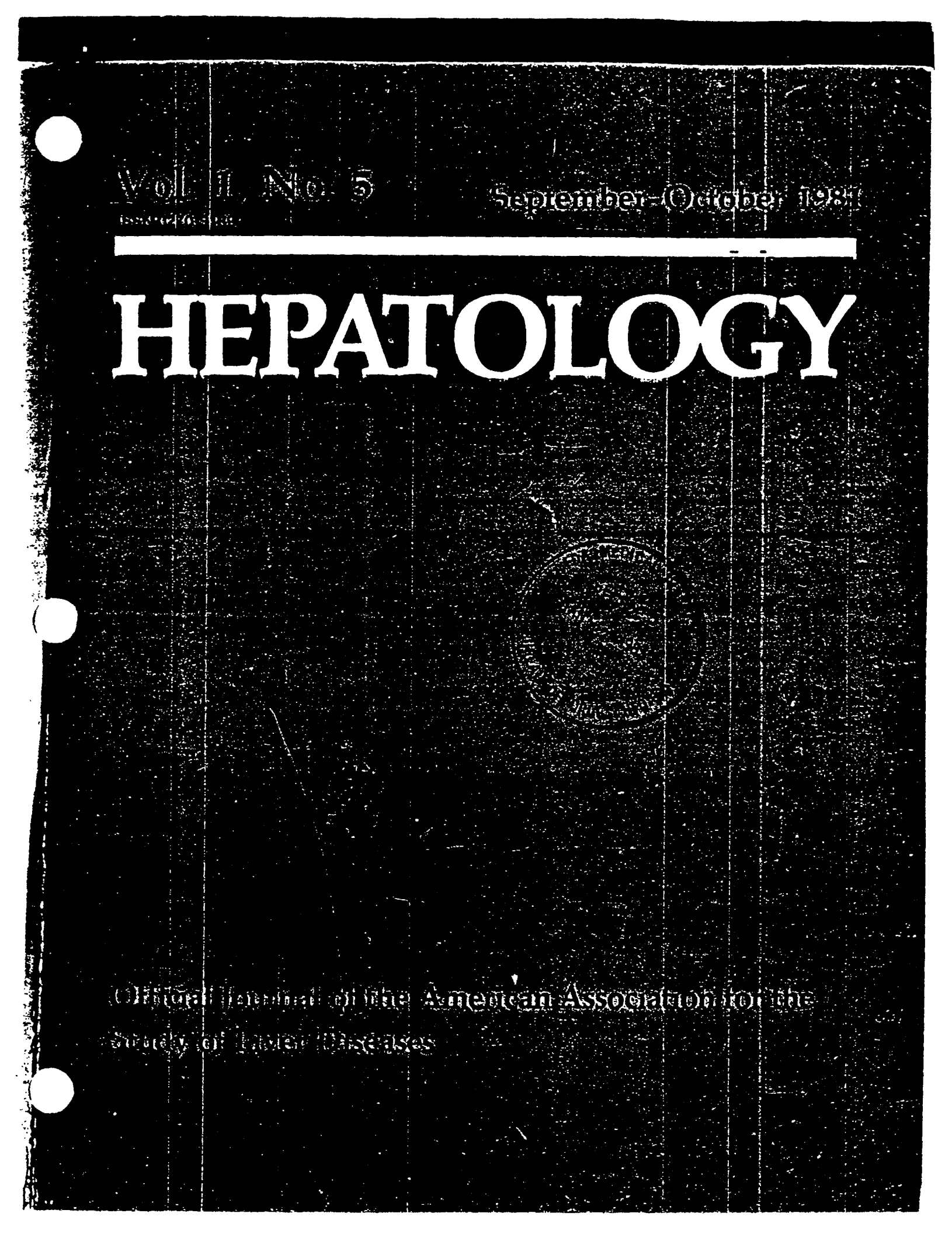
Concurrences:
HFD-530/DivisionDirector/HJolson
HFD-530/TLMO/

CC:
HFD-530/DepDivDir/DBirnkrant
HFD-530/NDA 20-903
HFD-530/Division File
HFD-530/Pharm/DMorse
HFD-530/Biopharm/PRajagopalan
HFD-530/Chemistry/RKambhampati
HFD-530/Micro/NBattula
HFD-730/GSoon
HFD-344/DSI/AEl Hage
HFD-530/CSO/TCrescenzi
HFD-530/ClinRev/RFleischer
HFD-530/MO/TNguyen

APPENDIX A

Vol. 1, No. 5 September-October 1981

HEPATOLOGY



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Formulation and Application of a Numerical Scoring System for Assessing Histological Activity in Asymptomatic Chronic Active Hepatitis

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A Histology Activity Index has been developed which generates a numerical score for liver biopsy specimens obtained from patients with asymptomatic chronic active hepatitis. Biopsies are graded in four categories: periportal necrosis, intralobular necrosis, portal inflammation, and fibrosis. Under code, three pathologists and three hepatologists evaluated 14 liver biopsy specimens obtained from five patients with asymptomatic chronic active hepatitis. Good correlation was seen between severity of liver biopsy lesions as judged by conventional histological descriptions and Histology Activity Index scores. Significant differences in Histology Activity Index score occurred in only 2 of 28 duplicate scorings of biopsy specimens by two observers. This system provides definitive endpoints for statistical analysis of serial changes in liver histology and offers an alternative to the use of conventional pathological descriptions in following the natural history and treatment responses of asymptomatic chronic active hepatitis.

Chronic active hepatitis (CAH) is a necroinflammatory lesion of the liver diagnosed by characteristic pathologic changes in the liver biopsy specimen. Early reports of patients with CAH emphasized the profound clinical and biochemical alterations often accompanying this condition, described the poor prognosis associated with severe CAH, and outlined treatment regimens which significantly decreased mortality and morbidity (2–5). Recently it has become apparent that patients with severe CAH represent only a small percentage of the total population whose liver biopsy specimen is interpreted as showing CAH (6, 7). Many such patients are totally free of clinical symptoms and have only mild alterations in serum aminotransferases, bilirubin, and γ-globulin. The natural history of asymptomatic CAH is not known and guidelines for treatment have not yet been established. The rate of clinical progression of asymptomatic CAH appears to be slower than for severe CAH. Conventional clinical events used in evaluating the natural history and response to treatment of severe CAH (such as death and development or disappearance of jaundice, ascites, and encephalopathy) will not be applicable in the study of asymptomatic CAH. Rather it appears that pathological study of serial liver biopsy specimens will be the most valuable parameter to follow the short-term course of this disease. Conventional pathological descriptions of histology of serial liver biopsy specimens are often extremely detailed or very broad and minimally descriptive. Such descriptions also do not readily provide definitive endpoints for statistical analysis. This report describes a Histology Activity Index (HAI) which generates a numerical score for asymptomatic CAH liver biopsy specimens. This scoring system is both objective and reproducible, and it may

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This study was supported by the Veterans Administration Cooperative Studies Program. Results of this study were presented at the annual meeting of the American Society for the Study of Liver Disease, Chicago, Illinois, November 1980, and have appeared in abstract form (1).
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be useful as either an alternative or supplement to the use of conventional pathological terminology in the study and management of asymptomatic CAH patients in whom histological changes in serial liver biopsy specimens may be the only prognostic indicator available for evaluation.

MATERIALS AND METHODS

Liver biopsy specimens for analysis were obtained from five patients whose serum aminotransferases had been elevated a mean period of 17 ± 8 months (range 8 to 27 months). Mean levels of serum SGOT and SGPT elevations were 58 ± 43 and 140 ± 178 mIU per ml, respectively (range 18 to 130 and 25 to 497 mIU per ml, respectively). No patient had persistent malaise, fatigue, or anorexia. None of the patients had jaundice, ascites, or encephalopathy, and γ-globulin elevations, if present, were minimal (mean 2.0 ± 0.4 gm per dl, range 1.4 to 2.6 gm per dl). One patient's serum was positive for HBsAg, HBeAg, and DNA polymerase, while the remaining four patients are presumed to be cases of non-A, non-B chronic hepatitis. The initial biopsy specimen was interpreted by one of the authors (K. G. I.) and a diagnosis of CAH was made. From one to three subsequent liver biopsy specimens were obtained in the patients over periods of 1 to 3 years. A total of 14 biopsy specimens was used in testing the applicability and reproducibility of the HAI scoring system.

Liver biopsies were performed percutaneously or at laparoscopy using a Travenol Tru-cut biopsy needle (Travenol Laboratories, Inc., Deerfield, Ill.). All biopsy specimens except two were ≥2 cm in length and contained ≥6 portal areas for examination. Specimens were fixed in 10% buffered formalin. Six to eight sections were cut from each biopsy for routine and special stains, but only sections stained with hematoxylin and eosin and Masson's trichrome stain were used in evaluating the scoring system. After coding, specimens were submitted to three hepatic pathologists and to three clinical hepatologists for their conventional interpretation and for numerical scoring according to the HAI. No training in, or discussion of, the HAI was provided to readers prior to scoring the biopsy specimens. All six readers saw the same sections of each liver biopsy specimen. To test the HAI scoring system for intraobserver variation, two of the authors (R. G. K. and K. G. I.) scored the coded biopsies on two occasions separated by a period of 1 to 2 months. Consistent differences in interobserver and intraobserver HAI scoring were tested for significance by analysis of variance (8).

A description of the HAI is given in Table 1. Biopsy

TABLE 1. HAI FOR NUMERICAL SCORING OF LIVER BIOPSY SPECIMENS[a]

I. Periportal +/− bridging necrosis	Score	II. Intralobular degeneration and focal necrosis[b]	Score	III. Portal inflammation	Score	IV. Fibrosis	Score
A. None	0	A. None	0	A. No portal inflammation	0	A. No fibrosis	0
B. Mild piecemeal necrosis	1	B. Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in <⅓ of lobules or nodules)	1	B. Mild (sprinkling of inflammatory cells in <⅓ of portal tracts)	1	B. Fibrous portal expansion	1
C. Moderate piecemeal necrosis (involves *less* than 50% of the circumference of most portal tracts)	3	C. Moderate (involvement of ⅓–⅔ of lobules or nodules)	3	C. Moderate (increased inflammatory cells in ⅓–⅔ of portal tracts)	3	C. Bridging fibrosis (portal-portal or portal-central linkage)	3
D. Marked piecemeal necrosis (involves *more* than 50% of the circumference of most portal tracts)	4	D. Marked (involvement of >⅔ of lobules or nodules)	4	D. Marked (dense packing of inflammatory cells in >⅔ of portal tracts)	4	D. Cirrhosis[c]	4
E. Moderate piecemeal necrosis *plus* bridging necrosis[d]	5						
F. Marked piecemeal necrosis *plus* bridging necrosis[d]	6						
G. Multilobular necrosis[e]	10						

[a] HAI score is the combined scores for necrosis, inflammation, and fibrosis.
[b] Degeneration—acidophilic bodies, ballooning; focal necrosis—scattered foci of hepatocellular necrosis.
[c] Loss of normal hepatic lobular architecture with fibrous septae separating and surrounding nodules.
[d] Bridging is defined as ≥2 bridges in the liver biopsy specimen; no distinction is made between portal-portal and portal-central linkage.
[e] Two or more contiguous lobules with panlobular necrosis.

specimens were graded in four categories: (a) periportal +/− bridging hepatocellular necrosis; (b) intralobular degeneration and focal hepatocellular necrosis; (c) portal inflammation, and (d) fibrosis. A numerical score for each category was assigned to each liver biopsy specimen, and the combined score of the four categories formed the HAI score for that biopsy specimen. The numerical score assigned each component in the HAI represented a consensus of the authors and was based on clinical experience and a review and critical analysis of literature pertinent to CAH histology (9–11). Periportal necrosis ± bridging necrosis was weighted more heavily than other parameters since it appears to be more influential in determining the activity and severity of severe CAH (10, 11). Also sampling variability for fibrosis, particularly in regard to cirrhosis, may be marked with serial liver biopsies (12).

RESULTS

Good correlation was seen between conventional histological descriptions for liver biopsy specimens from patients with asymptomatic CAH and HAI numerical scores (Figure 1). Liver biopsy specimens which were interpreted as showing chronic persistent hepatitis or nonspecific changes had low numerical scores, while biopsies with more severe liver lesions including CAH, CAH with bridging, and active cirrhosis had higher HAI scores. No examiner had difficulty adapting to the HAI scoring system. Mean standard deviation for interobserver differences in HAI scoring of the 14 biopsies was 2.4 and differences in scoring by the six readers did not approach statistical significance when tested by analysis of variance ($df_1 = 5$, $df_2 = 78$, $F = 0.788$). Intraobserver variation in HAI scores when biopsy specimens were interpreted on two different occasions by the same observer was also small (Figure 2). Mean difference in HAI score for 28 duplicate readings was 1.3 and the magnitude of this difference was not related to the size of the biopsy score. A difference of >3 in HAI score was seen in only 2 of 28 duplicate determinations (7%) and was paralleled by differences in the conventional reading (CAH vs. chronic persistent hepatitis for higher and lower scores, respectively). Both specimens with HAI scoring differences >3 had marginally adequate tissue available for examination; one specimen was fragmented and had only three portal areas for examination, while the second specimen was 1.5 cm in length and contained four portal triads. Differences in duplicate HAI scoring of biopsy

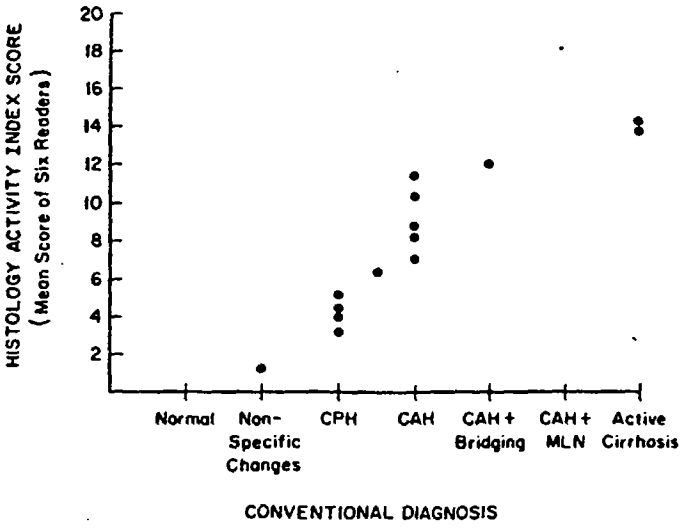

FIG. 1. Comparison of conventional readings for liver biopsy specimens with HAI scores. HAI values represent the mean score of six individual readers. The conventional diagnosis plotted was used for that particular liver biopsy specimen by four or more of the six examiners; in one instance, both chronic persistent hepatitis (CPH) and CAH were selected by three examiners and the biopsy result is plotted between these two conventional diagnoses.

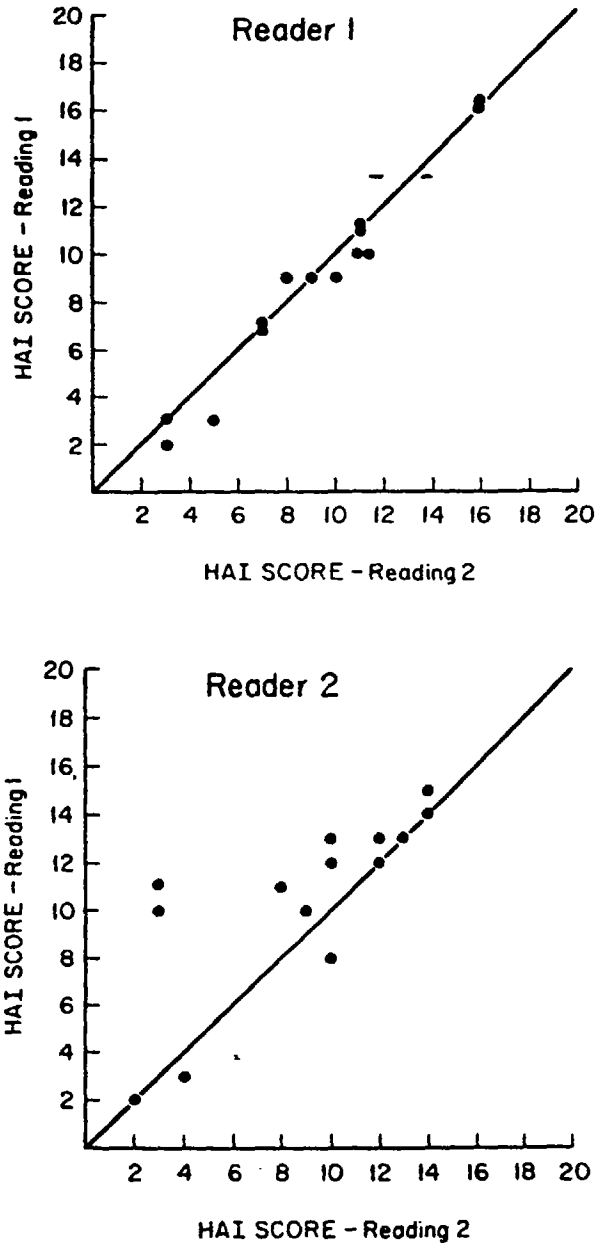

FIG. 2. Comparison of HAI scoring of liver biopsy specimens on duplicate determinations by two different readers. Biopsy scores for the initial reading are plotted against biopsy scores obtained at the second reading. Biopsies which were scored identically on the two determinations fall on the *solid diagonal line*. Reader 1, K. G. I.; Reader 2, R. G. K.

specimens by the same individual were not statistically significant (paired t test).

DISCUSSION

The importance of initial liver histology in predicting the evolution and response to treatment in severe CAH has been addressed by Baggenstoss and coworkers (10, 13). Severe histological disease activity (CAH + bridging, CAH + multilobular necrosis, and active cirrhosis) is associated with higher mortality rate and treatment failure. It is reasonable to assume that histological changes in serial liver biopsy specimens will also be an important parameter to follow in evaluating patients with asymptomatic CAH. Indeed, it may be the only parameter available for analysis in many such patients in whom no clinical or physical signs of chronic liver disease are present and whose liver biochemistries are minimally abnormal. If disease activity in asymptomatic CAH is to be assessed by changes in histology of serial liver biopsy specimens, such changes should be simply and objectively quantitated and should be easily amenable to statistical analysis. Conventional terminology used to describe severe CAH would be difficult to analyze statistically in asymptomatic CAH because it tends to use very detailed descriptive terms (14) or combines all lesions into four broad categories of CAH, CAH + bridging, CAH + multilobular necrosis, and active cirrhosis (10, 13).

The HAI developed in this paper provides an alternative to use of traditional terminology to describe liver histology in asymptomatic CAH. Numerical HAI scores paralleled severity of liver lesions as described by conventional terminology. High HAI scores were seen for liver biopsy specimens whose conventional diagnoses were CAH, CAH with bridging, and active cirrhosis, while low scores were seen with diagnoses of CPH and nonspecific changes. Overall HAI scores can also be broken into individual components of necrosis, inflammation, and fibrosis to yield additional information not provided by conventional composite scales for grading necroinflammatory liver disease (10, 11).

Total unanimity of liver biopsy assessment was not achieved by the six individual readers with conventional interpretation. All six readers made the same conventional diagnosis for only one of the 14 biopsies. The same diagnosis was made by four or more readers for 12 additional biopsies, while three readers selected the same diagnosis for the remaining biopsy specimen. The four categories chosen for inclusion in the HAI were piecemeal necrosis, intralobular degeneration and hepatocellular necrosis, portal inflammation, and fibrosis. Recently Theodossi et al. assessed 27 pathologic features for interobserver variation using Kappa statistics (15). High significance and strong evidence of agreement were seen between readers for piecemeal necrosis, intralobular necrosis and fibrosis, thus supporting the choice of categories included in the HAI scoring system. Standard deviation in HAI scoring of the 14 biopsies by the six readers was 2.4, and degree of variation in HAI scoring did not correlate well with magnitude of mean HAI scores (r^2 = 0.31). Interobserver variation in interpretation of liver biopsy histology using the HAI compares favorably with that seen using conventional terminology.

The degree of reproducibility of multiple interpretations of the same biopsy by one individual is an important characteristic of any system for describing liver histology. Intraobserver variability using the HAI scoring system approximated that of conventional interpretation both in this study and in the study by Soloway (12). Thirty-four slides of liver tissue obtained from patients with severe CAH were compared in Soloway's study, and overall severity of hepatitis was reproduced in 88% of duplicate interpretations using a grading scale of 0 (normal) to 3 (most severe). Standard deviation for intraobserver differences in HAI score between 28 duplicate readings in this study was 1.3. HAI scores for 24 of 28 duplicate determinations (86%) fell within 2 times the standard deviation (±2.6) of each other and 100% of 14 duplicate HAI interpretations by the more experienced reader (K. G. I.) differed by ±2 or less.

If liver histology does not change in asymptomatic CAH patients during a reasonable period of observation, then histology will not be a helpful parameter to follow in the assessment of this disease. The fourteen serial biopsy specimens obtained over a 1- to 3-year period from the five asymptomatic CAH patients are grouped by patient in Table 2. A ±4 change in HAI scoring of biopsy specimens by the same observer, 3 times the standard deviation seen for 28 duplicate liver biopsy readings, was chosen as the level indicating a high probability that actual improvement or worsening in liver histology had occurred. Liver histology in 4 of the 5 asymptomatic CAH patients showed a >±4 change in HAI scoring over the 1- to 3-year period of observation.

No data are available as to whether HAI scores more accurately predict clinical prognosis of asymptomatic CAH than conventional pathological descriptions. Anecdotally, HAI scoring suggested a progressing liver le-

TABLE 2. HAI SCORES FOR SERIAL LIVER BIOPSY SPECIMENS FROM PATIENTS WITH ASYMPTOMATIC CAH[a]

Patient	Date of biopsy	HAI score
N. P.	1977	15
	1978	13
	1979	9
R. M.	1977	8
	1978_1	9
	1978_2	11
	1979	14
P. C.	1975	7
	1976	10
	1978	8
A. A.	1977	7
	1979	1
E. G.	1978	12
	1979	5

[a] Biopsy specimens scored by R. G. K. Biopsies were coded and scorer was blinded as to patient identity, time sequence of biopsy, and treatment regimens at time of biopsy interpretation.