CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

STATISTICAL REVIEW(S)

HFD 530/Crescenzi

MAY 27 1998

Statistical Review and Evaluation

NDA#:	20-903
APPLICANT:	Schering Corporation
NAME OF DRUG:	Rebetol™ (ribavirin) Capsules
INDICATION:	Treatment of Chronic Hepatitis C
DOCUMENTS REVIEWED:	3.1, 3.2, 3.169-3.294, CANDA (12/03/97)
MEDICAL INPUT:	HFD-530: R. Fleischer, PA. C, MPH
	HFD-530: T. Nguyen, M.D.

A. Background

This NDA contains four pivotal, independent, multicenter trials (2 U.S. and 2 International) to support the proposed indication for the treatment of chronic hepatitis C. Efficacy was evaluated based upon C95-144 (U.S. trial) and I95-145 (International trial) which were two identical studies for patients with chronic hepatitis C who responded to initial treatment of interferon and relapsed thereafter. The summary of safety was based on the above two studies reviewed for efficacy as well as a Phase I study (in patients with chronic hepatitis C), a Phase II study (in patients with chronic hepatitis C not previously treated) and the two ongoing Phase III studies. In this review, only studies C95-144 and I95-145 will be reported.

Protocols C95-144 and 195-145

Title: "Intron® A Monotherapy vs. Intron® A+Ribavirin for Treatment of Relapse in Patients with Chronic Hepatitis C "

Both protocols were double-blind, placebo-controlled, multicenter, randomized, parallel group trials comparing two treatment strategies in patients with compensated chronic hepatitis C who responded to one or two courses of alpha interferon and who had relapsed (based upon ALT > ULN) after the most recent course of alpha interferon therapy. Approximately one hundred and fifty (150) patients on each protocol were to be enrolled at about 15 study sites with an estimated 10 patients at each site. Patients were to be equally randomized using a centralized randomization procedure described by Pocock and Simon (1975) to receive either Intron A + placebo for 24 weeks or Intron A + ribavirin for 24 weeks. This randomization procedure was designed to balance the treatment groups with respect to the following baseline characteristics:

- pretreatment liver histology (cirrhosis or no cirrhosis);
- serum HCV status (HCV ≤2,000,000 copies/mL or >2,000,000 copies/mL); and
- HCV genotype (I or other).

Patients had clinical visits at weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24 during treatment and at weeks 4, 8, 12 and 24 during the follow-up period. Serum HCV RNA/qPCR was to be evaluated at weeks 4, 12 and 24 during treatment and at weeks 12 and 24 following the end of therapy. A liver biopsy was to be done at baseline and after 24 weeks of treatment free follow-up.

The primary efficacy endpoint for this study is the overall response defined below. The primary objective was to compare Intron A + Ribavirin with Intron A + Placebo at 24 weeks of follow-up (i.e., study week 48) with respect to overall response. Sustained response at 24 weeks of follow-up was also of interest.

Responder: a patient was classified as a virologic responder at a given time point if the HCV RNA was below the reported lower limit of quantification (LOQ) of the serum PCR assay at that time point.

Sustained responder: a patient was a sustained responder if his/her serum HCV RNA was below LOQ at the end of follow-up (i.e., study week 48). Specifically, a sustained responder completed at least 141 days of follow-up and had no HCV RNA above LOQ between 141 and 196 days of follow-up. If a patient had no HCV RNA evaluations between 141 and 196 days of follow-up, the first HCV RNA evaluation after 196 days of follow-up had to be below LOQ.

Overall response: each patient's overall response status was classified as: overall responder, overall non-responder, or missing. A patient was classified as an overall responder if he/she was a sustained virologic responder and his/her post-treatment liver biopsy score (Knodell score components I, II and III) improved by 2 or more units relative to the pre-treatment score. A patient was an overall non-responder if he/she was not a sustained virologic responder and/or the post-treatment liver score did not improve by 2 or more units relative to the pre-treatment score. Finally, a patient's overall response was classified as missing if he/she was a sustained virologic responder but the liver score could not be determined.

B. Results of the Applicant's Analyses

Study C95-144

Study C95-144 started in April, 1996 and ended in June, 1997. One-hundred and fifty-four (154) were randomized and 153 treated: 77 treated with Intron A plus ribarivin and 76 treated with Intron A plus placebo.

The primary efficacy analysis of the overall response rate was based on the intent-to-treat approach using a logistic regression model with main effects due to treatment, genotype, presence of cirrhosis, and baseline HCV RNA. In this analysis, subjects with missing HCV RNA evaluations were regarded as non-sustained HCV RNA responders and therefore non-overall responders. However, for subjects whose HCV RNA levels were below LOQ at Week 48 and whose biopsy changes were missing, the missing biopsy was assumed to be non-informative in the sense that, for a given combination of covariates, these subjects had the same chance of being biopsy responders as those subjects with biopsy scores available. For this analysis, the main effects were estimated by a maximum likelihood-based method (MLE). In this analysis, the sustained response was also modeled by the same logistic regression procedure which incorporated the same independent variables as the overall response analysis. Comparability of the treatment groups at baseline was assessed using Fisher's exact test.

Baseline Characteristics

A total of 153 patients were treated in the study with median age 43 years (range from 28 to 67). The two treatment groups were similar at baseline in demographic characteristics. The disease profile in both treatment groups was similar.

Patient Accountability

The following figure presents the disposition of patients for study C95-144.

Patient Status and Reason Discontinued by Treatment Group for Study C95-144

Patient Status	Intron A + Ribavirin n=77	Intron A + Placebo n=76	~~Total~~ n=153
Completing both study treatment and follow-up	**64 (83%)**	**67 (88%)**	**131**
Total patients discontinued	**13 (17%)**	**9 (12%)**	**22**
Discontinued during study treatment	10 (13%)	5 (7%)	15
Adverse events	7 (9%)	3 (4%)	10
Patient refusal to continue	2 (3%)	2 (3%)	4
Noncompliance	1 (1%)	0 (0%)	1
Discontinued during follow-up	3 (4%)	4 (5%)	7
Patient lost to further follow-up	1 (1%)	1 (1%)	2
Adverse events	0 (0%)	1 (1%)	1
Patient refusal to continue	1 (1%)	2 (3%)	3
Noncompliance	1 (1%)	0 (0%)	1

Efficacy Endpoints

The primary efficacy variable for this study is the overall response rate at the end of follow-up (24 weeks following the end of treatment), which is a composite of the loss of serum HCV RNA and change in liver histology at the end of follow-up. The applicant analyzed both the combined endpoint (overall response) and its components (sustained response and liver biopsy score). The results are summarized below.

Sustained Response

The proportion of patients with HCV RNA below LOQ at the end of follow-up was greater ($p<0.0001$) in the patients treated with the combination of Intron A plus ribavirin compared to those receiving Intron A plus placebo. The following table presents the end of follow-up HCV RNA response for all treated patients.

HCV RNA at Week 48 for Study C95-144

PCR Response at Week 48	Intron A + Rebarivin N=77	Intron A + Placebo N=76	p-value
HCV RNA below LOQ	34 (44.2%)	3 (3.9%)	<0.0001
HCV RNA above LOQ	34 (44.2%)	64 (84.2%)	
Missing	9 (11.7%)	9 (11.8%)	

Liver Biopsy Score

Pre- and post-treatment biopsies were available for 79% (61/77) of the patients treated with Intron A plus ribavirin and of 84% (64/76) of those patients who received Intron A plus placebo. The following table summarizes the treatment effect on hepatic inflammation (sum of categories I+II+III) for patients with both pre- and post-treatment liver biopsy results. The proportion of patients with improvement (decrease of 2 or more based on Knodell HAI score) in liver inflammation was significantly greater (p=0.032) in patients receiving Intron A plus ribavirin compared to those receiving Intron A plus placebo. The following table summarizes the results.

Liver Biopsy Improvement at Week 48 from Baseline for Study C95-144

Change in Histology	Intron A + Ribavirn (n=61)	Intron A + Placebo (n=64)	p-value
Improved Biopsy	38 (62%)	27 (42%)	0.032
Not Improved	23 (38%)	37 (58%)	
No change	15 (25%)	20 (31%)	
Worse	8 (13%)	17 (27%)	

Overall Response

The following table presents the cross tabulation of HCV RNA response status and liver improvement in Knodell inflammation score (biopsy) at 24 weeks post treatment by treatment group.

HCV RNA at Week 48 and Biopsy Improvement for Study C95-144 (n)

	Biopsy Improvement (I+II+III)							
	Intron A + Ribavirin				Intron A + Placebo			
PCR at 24 weeks post treatment	Yes	No	Missing	All	Yes	No	Missing	All
Below LOQ	25	5	4	34	2	1	0	3
Above LOQ	13	18	3	34	25	36	3	64
Missing	0	0	9	9	0	0	9	9
All	38	23	16	77	27	37	12	76

The overall response is summarized in the following table based on the following analyses: 1) maximum likelihood estimate (MLE) for all treated patients; 2) patients with complete biopsy data (patients with missing HCV RNA data classified as non-responders); and 3) patients with missing data (missing HCV RNA/biopsy or both) classified as non-responders. The overall response rate in the Intron A plus ribvarin treatment group was significantly greater (p<0.0001) than that observed in the Intron A plus placebo group for all methods of evaluation.

Overall Response Rate for Study C95-144

Methods of Analysis	Intron A + Ribvarin	Intron A + Placebo	p-value
Maximum Likelihood Estimate	36.5%	2.7%	<0.0001
Patients with complete biopsy data	41.0% (25/61)	3.1% (2/64)	<0.0001
Treat patients with missing data as failures	32.5% (25/77)	2.6% (2/76)	<0.0001

Study I95-145

Study I95-145 started in April, 1996 and ended in July, 1997. One-hundred and ninety-five patients were randomized and 192 treated: 96 treated with Intron A plus ribarivin and 96 treated with Intron A plus placebo.

Baseline Characteristics

A total of 192 patients were treated in the study with median age 44 years (range from 23 to 76). The two treatment groups were similar at baseline in demographic characteristics. The disease profile in both treatment groups was similar.

Patient Accountability

The following figure presents the disposition of patients for study I95-145 of those starting therapy.

Patient Status and Reason Discontinued by Treatment Group for Study I95-145

Patient Status	Intron A + Ribavirin n=96	Intron A + Placebo n=96	Total n=192
Completing both study treatment and follow-up	**90 (94%)**	**92 (96%)**	**131**
Total patients discontinued	**6 (6%)**	**4 (4%)**	**10**
Discontinued during study treatment	4 (4%)	2 (2%)	6
Adverse events	3 (3%)	2 (2%)	5
Noncompliance	1 (1%)	0 (0%)	1
Discontinued during follow-up	2 (2%)	2 (2%)	4
Death	0 (0%)	1 (1%)	1
Patient lost to further follow-up	2 (2%)	1 (1%)	3

Efficacy Endpoints

Similar to Study C95-144, the applicant analyzed both the combined endpoint (overall response) and its components (sustained response and liver biopsy score). The results are summarized below.

Sustained Response

The proportion of patients with HCV RNA below LOQ at the end of follow-up was greater ($p<0.0001$) in patients treated with the combination of Intron A plus ribavirin compared to those receiving Intron A plus placebo. The following table presents the end of follow-up HCV RNA response for all treated patients.

HCV RNA at Week 48 for Study I95-145

PCR Response at Week 48	Intron A + Rebarivin N=96	Intron A + Placebo N=96	p-value
HCV RNA below LOQ	50 (52.1%)	5 (5.2%)	<0.0001
HCV RNA above LOQ	41 (42.7%)	88 (91.7%)	
Missing	5 (5.2%)	3 (3.1%)	

Liver Biopsy Score

Pre- and post-treatment biopsies were available for 81%(78/96) of the patients treated with Intron A plus ribavirin and of 77% (74/96) of those patients who received Intron A plus placebo. The following table summarizes the treatment effect on hepatic inflammation (sum of categories I+II+III) for patients with both pre- and post-treatment liver biopsy results. The proportion of patients with improvement (decrease of 2 or more based on Knodell HAI score) in liver inflammation was significantly greater ($p=0.009$) in patients receiving Intron A plus ribavirin compared to those receiving Intron A plus placebo. The following table summarizes the results.

Liver Biopsy Improvement at Week 48 from baseline for Study I95-145

Change in Histology	Intron A + Ribavirn (n=78)	Intron A + Placebo (n=74)	p-value
Improved Biopsy	49 (63%)	30 (41%)	0.009
Not Improved	29 (37%)	44 (59%)	
No change	21 (27%)	28 (38%)	
Worse	8 (10%)	16 (22%)	

Overall Response

The following table presents the cross tabulation of HCV RNA response status and liver improvement in Knodell inflammation score (biopsy) at 24 weeks post treatment by treatment group.

HCV RNA at Week 48 and Biopsy Improvement for Study I95-145 (n)

	Biopsy Improvement (I+II+III)							
	Intron A + Ribavirin				Intron A + Placebo			
PCR at 24 weeks post treatment	Yes	No	Missing	All	Yes	No	Missing	All
Below LOQ	39	8	3	50	4	0	1	5
Above LOQ	10	21	10	41	26	44	18	88
Missing	0	0	5	5	0	0	3	3
All	49	29	18	96	30	44	22	96

The overall response is summarized in the table below. The overall response rate in the Intron A plus ribvarin treatment group was significantly greater ($p<0.0001$) than that observed in the Intron A plus placebo group for all methods of evaluation.

Overall Response Rate for Study I95-145

Methods of Analysis	Intron A + Ribvarin	Intron A + Placebo	p-value
Maximum Likelihood Estimate	42.7%	5.2%	<0.0001
Patients with complete biopsy data	50.0% (39/78)	5.4% (4/74)	<0.0001
Treat patients with missing data as failures	40.6% (39/96)	4.2% (4/96)	<0.0001

C. Statistical Reviewer's Comments

There was one patient in Study C95-144 who was randomized to the Intron A + Placebo group but actually took Intron A + Ribavirin. This patient was included in the latter arm in the applicant's efficacy analysis. Since this patient was both a virologic and biopsy non-responder, it should cause no concern for the efficacy analysis.

In the protocol, a subject was defined to be a sustained HCV RNA responder if the viral load was below LOQ at Week 48. Based upon the recommendation of the medical reviewer, an alternative definition of sustained response was used. The new definition requires the subject to have HCV RNA below LOQ at Weeks 24, 36 and 48. Analysis based on the new definition will be presented in the next section.

The applicant's primary efficacy analysis for overall response was based on a logistic regression model with treatment and the three stratification variables as covariates. A maximum likelihood estimation (MLE) method was used to estimate the treatment effects. In this analysis, patients whose overall response status could not be determined due to missing biopsy evaluations could contribute to the analysis. However, this analysis assumes that the missing data occurred at random which may not be justifiable. Additionally, the original NDA was model based which raised concerns because it did not take the special randomization procedure employed in assigning patients to treatment groups into consideration. The applicant's supplemental use of bootstrapping did not adequately address this issue because it randomly sampled the subjects which ignores the sequential nature of the assignment. However, the observed treatment effects were large enough for the overall response and sustained response in these studies such that different ways of testing the treatment effects should make little difference. As will be shown, the biopsy results are sensitive to assumptions made regarding missing data. The missing data is substantial enough that the effect of the particular randomization procedure is of lesser importance. In the reviewer's analyses below, only simple proportions will be used for estimation and comparison. Sensitivity analyses will also be carried out to assess the impact of missing data on the statistical conclusions.

The HCV RNA assay was considered to be qualitative only and its claimed lower limit of quantification of 100 copies/mL was not substantiated in the submission. As there was a clear separation between responders and non-responders, the particular lower limit used will have little or no impact upon the study conclusions. See the Microbiology Review for details.

D. Statistical Reviewer's Analyses

D1. Sustained HCV RNA Response

If a patient whose HCV RNA is below LOQ at Weeks 24, 36 and 48, then this patient is considered to be a sustained HCV RNA responder. Due to patterns of missing data, a number of patients were difficult to classify, The following table shows the patterns of data:

Sustained HCV RNA Response (n)

						144 Placebo	144 Ribavirin	145 Placebo	145 Ribavirin
Sustained Responder						3	32	5	45
Non-responder						66	36	91	46
Uncertain						7	9	0	5
			Week						
Cases	4	12	24	36	48				
1.	X	X	*	*	*	6	5	0	2
2.	+	X	-	*	*	1	2	0	1
3.	+	-	*	-	*	0	1	0	0
4.	-	-	-	-	*	0	0	0	1
5.	-	-	-	*	-	0	1	0	0
6.	*	-	*	-	-	0	0	0	1

"*" stands for missing value, "+" stands for > LOQ and "-" stands for < LOQ. "X" could be <LOQ, >LOQ or missing

In cases of missing values, the review team agreed that only the subject in case 5 listed above will be regarded as a sustained HCV RNA responder. The analysis of proportions is summarized in the next table:

Sustained HCV RNA Response Rate

	Intron A + Placebo	Intron A + Ribavirin	p-value
Study 144	3.9% (3/76)	42.9% (33/77)	<0.001
Study 145	5.2% (5/96)	46.9% (45/96)	<0.001

In the analysis above, all the unknowns except Case 5 were classified as non-sustained HCV RNA responders regardless of the treatment assignment. To assess the impact of different ways of classifying the unknowns, the worst-case scenario is analyzed below. In this analysis all unknowns in the Intron A + Ribavirin arm except Case 5 were still regarded as non-sustained HCV RNA responders while in the Intron A + Placebo arm they were regarded as sustained HCV RNA responders:

Sustained HCV RNA Response Rate: Worst Case

	Intron A + Placebo	Intron A + Ribavirin	p-value
Study 144	13.2% (10/76)	42.9% (33/77)	<0.001
Study 145	5.2% (5/96)	46.9% (45/96)	<0.001

Therefore, both trials demonstrated that Ribavirin added to Intron A suppresses HCV RNA in serum better than Intron A alone in the Intron relapse patients. This conclusion does not depend on any assumptions made on the missing data.

D2. Biopsy response

A patient is a biopsy responder if his/her biopsy score (I+II+III) decreased by 2 points or more from baseline after 24 weeks post-therapy follow-up. The biopsy response is summarized below:

Biopsy Response (n)

	144 Placebo	144 Ribavirin	145 Placebo	145 Ribavirin
Biopsy Responder	27	38	30	49
Non-responder	37	23	44	29
Uncertain	12	16	22	18

When unknowns are regarded as non-responders, the biopsy response rates are:

Biopsy Response Rate

	Intron A + Placebo	Intron A + Ribavirin	p-value
Study 144	35.5% (27/76)	49.4% (38/77)	0.065
Study 145	31.3% (30/96)	51.0% (49/96)	0.006

For Study 144, the difference in biopsy response rates between the two treatment groups is not statistically significant at 0.05 (p-value = 0.065). Recall that in the applicant's analysis, where all missing data were omitted, the p-value for the same analysis is 0.032.

For Study 145 this difference is statistically significant (p-value = 0.006). However, of the 22 subjects with missing biopsy score in the Intron A + Placebo arm, if 6 or more were regarded as biopsy responders while all other subjects with missing were regarded as non-responders, then the p-value is greater than 0.05.

Therefore, the conclusions on statistical significance depend upon how the missing values are handled. Due to the fairly high rates of missing data and small observed differences in biopsy response rates between the two treatment groups, a slightly less favorable interpretation of the missing data will cause the p-values to be greater than 0.05.

D3. Overall response

An overall responder is defined to be a subject who is both a sustained HCV RNA responder and a histologic responder. The following table shows the classification of subjects in the two studies:

Study 144: Sustained HCV RNA Response and Biopsy Improvement (n)

	Biopsy Improvement (Using the first three components of Knodell score)							
	Intron A + Ribavirin				Intron A + Placebo			
Sustained HCV RNA Response	Yes	No	Missing	Total	Yes	No	Missing	Total
Yes	23	5	4	32	2	1	0	3
No	14	18	4	36	25	36	5	66
Missing	1*	0	8	9	0	0	7	7
Total	38	23	16	77	27	37	12	76

* Case 5 in the first table of section D1.

Study 145: Sustained Virologic Response and Biopsy Improvement (n)

	Biopsy Improvement (Using the first three components of Knodell score)							
	Intron A + Ribavirin				Intron A + Placebo			
Sustained HCV RNA Response	Yes	No	Missing	Total	Yes	No	Missing	Total
Yes	35	7	3	45	4	0	1	5
No	14	21	11	46	26	44	21	91
Missing	0	1	4	5	0	0	0	0
Total	49	29	18	96	30	44	22	96

Since the patient marked with a * in the first table was considered to be a sustained responder in Section D1, and this patient improved in biopsy, this patient will be regarded as an overall responder. The overall response status can be summarized below:

Overall Response (n)

	144 Placebo	144 Ribavirin	145 Placebo	145 Ribavirin
Overall Responder	2	24	4	35
Non-responder	67	41	91	54
Uncertain	7	12	1	7

Therefore the overall response rates are:

Overall Response Rate

	Intron A + Placebo	Intron A + Ribavirin	p-value
Study 144	2.6% (2/76)	31.2% (24/77)	<0.001
Study 145	4.2% (4/96)	36.5% (35/96)	<0.001

The worst-case analysis is summarized below:

Overall Response Rate: Worst Case

	Intron A + Placebo	Intron A + Ribavirin	p-value
Study 144	11.8% (9/76)	31.2% (24/77)	0.003
Study 145	5.2% (5/96)	36.5% (35/96)	<0.001

Therefore the Ribavirin in combination with Intron A is more effective in treating Interferon experienced patients than with Intron A alone. The conclusion holds regardless of the manner in which missing data are interpreted.

D4. Subgroup analysis

The applicant conducted subgroup analyses on the randomization stratification variables including genotype, baseline HCV RNA and baseline cirrhosis/fibrosis status. The applicant also conducted subgroup analyses on gender, age, race and some other baseline variables. Only genotype and baseline HCV RNA were found to be associated with the treatment response. The following tables summarize the results based on the revised definition of sustained HCV RNA response. The applicant's result is similar and will not be presented in this review.

Subgroup Analysis by Genotype

Study	Genotype	Sustained HCV RNA response		Biopsy		Overall	
		Ribavirin	Placebo	Ribavirin	Placebo	Ribavirin	Placebo
144	Type I	26.0% (13/46)	2.4% (1/42)	39.1% (18/46)	38.1% (16/42)	15.2% (7/46)	2.4% (1/42)
	Non-type I	64.5% (20/31)	5.9% (2/34)	64.5% (20/31)	32.4% (11/34)	54.8% (17/31)	2.9% (1/34)
145	Type I	29.6% (16/54)	3.8% (2/53)	38.9% (21/54)	24.5% (13/53)	18.5% (10/54)	1.9% (1/53)
	Non-type I	69.0% (29/42)	7.0% (3/43)	66.7% (28/42)	39.5% (17/43)	59.5% (25/42)	7.0% (3/43)

We see from the table that the Non-genotype I patients responded better than genotype I patients regardless of the treatment received. This is particularly true for the Ribavirin treated patients where the nominal p-values for the differences of the overall response rates are less than 0.001 for both studies. However, no significant interactions were found between the treatment and

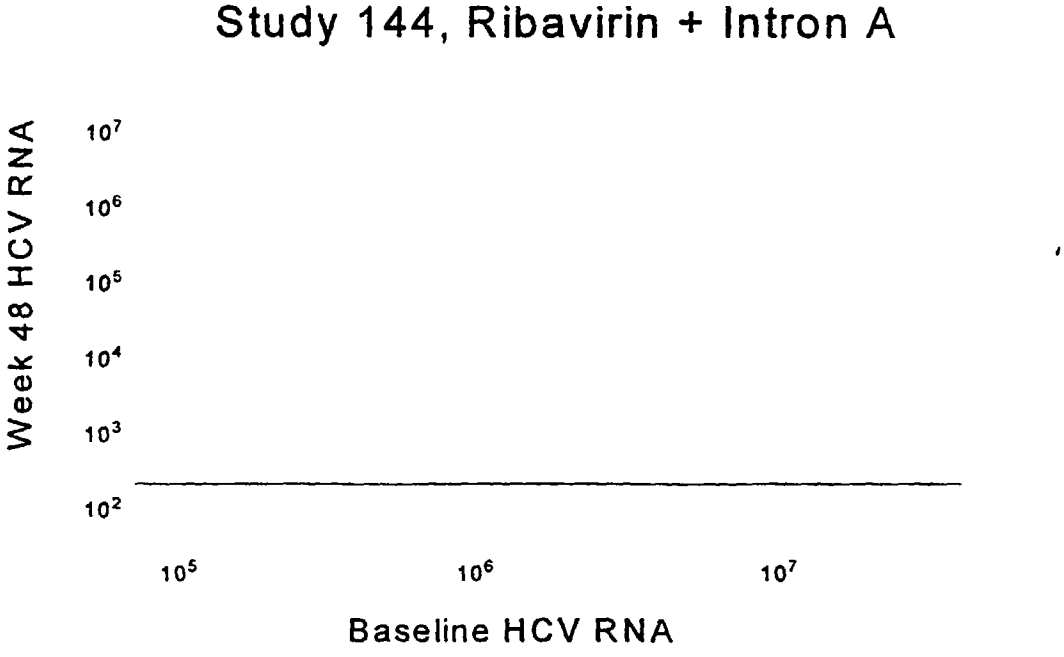
genotype. The p-values from the Breslow-Day test for the homogeneity of odds ratio are 0.256 for the Study 144 and 0.685 for the Study 145.

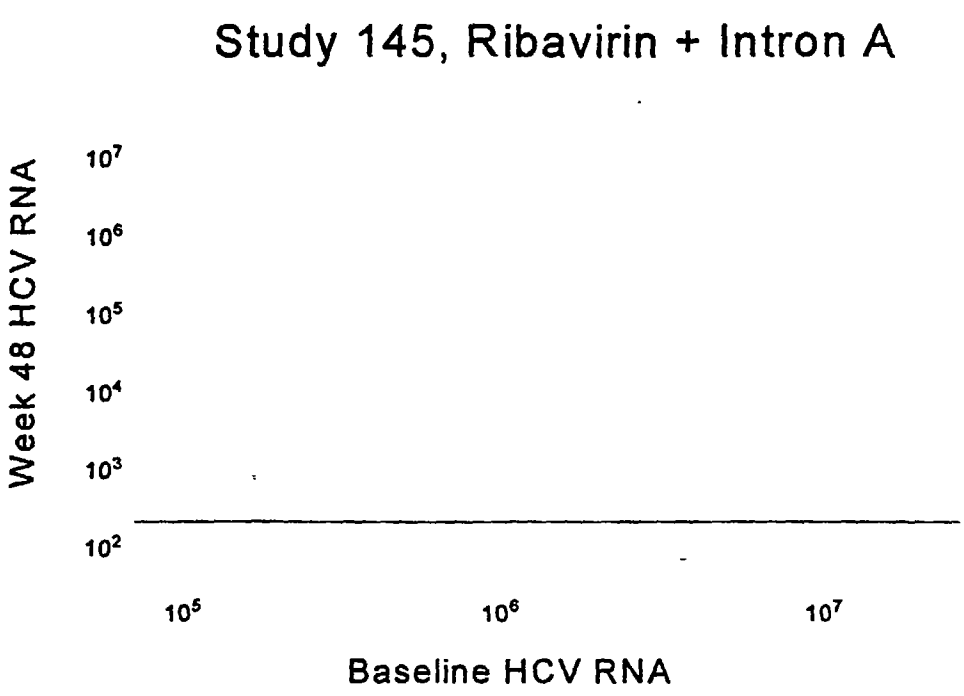
The table below summarizes the response rates by gender. As noted earlier, no significant treatment difference were found between males and females.

Subgroup Analysis by Gender

Study	Gender	Sustained HCV RNA response		Biopsy		Overall	
		Ribavirin	Placebo	Ribavirin	Placebo	Ribavirin	Placebo
144	Males	36.7% (18/49)	3.8% (2/53)	44.9% (22/49)	37.3% (20/53)	28.6% (14/49)	4.4% (1/23)
	Females	53.6% (15/28)	4.4% (1/23)	57.1% (16/28)	30.4% (7/23)	35.7% (10/28)	1.9% (1/53)
145	Males	46.0% (29/63)	8.5% (5/59)	54.0% (34/63)	32.2% (19/59)	38.1% (24/63)	6.8% (4/59)
	Females	48.5% (16/33)	0.0% (0/37)	45.5% (15/33)	29.7% (11/37)	33.3% (11/33)	0.0% (0/37)

The applicant's analysis of the effects of baseline HCV RNA on the final outcome was based on separating the patients into ≤ 2 million copies/mL and >2 million copies/mL. It was found that subjects with HCV RNA ≤ 2 million copies/mL had a better chance of achieving HCV RNA below LOQ at Week 48. The plot below shows the relationship of the baseline and Week 48 HCV RNA. It appears that the two variables are positively correlated but the correlation is weak.




Study 145, Ribavirin + Intron A
Week 48 HCV RNA
10^7
10^6
10^5
10^4
10^3
10^2
10^5
10^6
10^7
Baseline HCV RNA

E: Statistical Reviewer's Overall Assessment

Based on study 144 and 145, the following statistical conclusions can be drawn:

A significantly higher percentage of patients in the Ribavirin + Intron A group achieved overall response than those in the Placebo + Intron A group. Similar conclusions can be drawn for the sustained HCV RNA response. These conclusions hold regardless of how the missing data were regarded.

A higher percentage of patients in the Ribavirin + Intron A group achieved biopsy improvement than those in the Placebo + Intron A group. Overall, there is evidence that Ribavirin + Intron A treated patients responded better in biopsy than patients treated with Intron A alone. This conclusion is sensitive to assumptions made on missing data because of the smaller treatment effect with respect to biopsy, and the greater amount of missing biopsy data.

Greg Soon, Ph.D. 5/27/98
Mathematical Statistician

Concur: Dr. Flyer OF 5/27/98

cc:
Archival NDA #20-903
HFD-530
HFD-104/Ms. Townsend (via team links)
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