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CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTIVIRAL DRUGS ADVISORY COMMITTEE

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OPEN SESSION

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MONDAY, MAY 4, 1998

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ORIGINAL

The open session was held in Salons C and

D, Hilton Hotel, Gaithersburg, Maryland, at 8:30 a.m.,

Scott Hammer, M.D., Chair, presiding.

PRESENT:

SCOTT M. HAMMER, M.D.	Chair
RHONDA W. STOVER, RPh	Executive Secretary
WAFAA EL-SADR, MD, MPH	Member
JUDITH FEINBERG, MD	Member
JOHN D. HAMILTON, MD	Member
JAMES J. LIPSKY, MD	Member
ROGER J. POMERANTZ, MD	Member
JOSEPH S. BERTINO, JR., PharmD	Guest Consumer Representative

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PRESENT: (continued)

STEVE SELF, PhD	FDA Consultant
LAWRENCE S. FRIEDMAN, MD	FDA Guest
DAVID R. GRETCH, MD, PhD	FDA Guest
REGINA POLLICHINO, RN	Guest Patient Rep.
HYMAN ZIMMERMAN, MD	FDA Guest

FDA REPRESENTATIVES:

RACHEL BEHRMAN, MD, MPH  
RUSSELL FLEISCHER, PA-C, MPH  
HEIDI M. JOLSON, MD, MPH  
DIANNE MURPHY, M.D.  
TAN NGUYEN, MD, PhD  
GREG SOON, PhD

Sponsor Representatives:

JANICE K. ALBRECHT, PhD  
PENELOPE J. GILES, PhD

Public Comment:

MARY IANELLI  
VINOD RUSTGI, M.D.

ALSO PRESENT:

SUSANNAH CORT, MD  
PAUL GLUE, MD, PhD  
ZACHARY GOODMAN, MD  
GREG REYES, MD, PhD

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## P-R-O-C-E-E-D-I-N-G-S

(8:33 a.m.)

CHAIRMAN HAMMER: I'd like to ask everyone to take his or her seat. We're going to start in 30 seconds.

Good morning. I'd like to call this morning's session to order and welcome everyone, and particularly the sponsor, the Schering Corporation.

We're here today to discuss the application of Intron A in combination with Rebetol or Interferon alfa-b in combination with ribavirin for the treatment of chronic hepatitis C in relapse.

I'd like to turn to Rhonda Stover, who will read the conflict of interest statement.

MS. STOVER: Thank you. The following announcement addresses the issue of conflict of interest with regard to this meeting. It is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict

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1 of interest at this meeting.

2 With respect to FDA's invited guests, Dr.  
3 David Gretch has involvement which we believe should  
4 be made public to allow the participants to  
5 objectively evaluate his comments. Dr. Gretch would  
6 like to disclose that he is a paid consultant for  
7 Schering-Plough in the area of HCV therapy, and that  
8 he is a member of Schering's Speaker's Bureau.

9 In the event that the discussions involve  
10 any other products or firms not already on the agenda  
11 for which an FDA participant has a financial interest,  
12 the participants are aware of the need to exclude  
13 themselves from such involvement, and their exclusion  
14 will be noted for the record.

15 With respect to all other participants, we  
16 ask, in the interest of fairness, that they address  
17 any current or previous involvement with any firm  
18 whose products they may wish to comment upon.

19 CHAIRMAN HAMMER: Thank you. I'd like now  
20 to ask the members of the committee to introduce  
21 themselves for the record. I'll begin on my left with  
22 Dr. Gretch.

23 DR. GRETCH: Thank you. I'm David Gretch.  
24 I'm Director of the Viral Hepatitis Laboratory at the  
25 University of Washington Medical Center.

1 DR. FRIEDMAN: I'm Larry Friedman. I'm a  
2 gastroenterologist at the Massachusetts General  
3 Hospital and Harvard Medical School.

4 MS. POLLICHINO: I'm Gina Pollichino. I'm  
5 here as a patient representative. I'm an RN, and I'm  
6 also -- I run hepatitis C support groups.

7 DR. BERTINO: Joseph Bertino. I'm from  
8 the Clinical Pharmacology Research Center at Bassett  
9 Health Care in Cooperstown, New York, consumer rep.

10 DR. SELF: Steve Self, a biostatistician  
11 at Fred Hutcherson Cancer Research Center and  
12 University of Washington.

13 DR. EL-SADR: I'm Wafaa El-Sadr,  
14 infectious diseases at Harlem Hospital in New York.

15 CHAIRMAN HAMMER: Scott Hammer from the  
16 Beth Israel Deaconess Medical Center and Harvard  
17 Medical School in Boston.

18 MS. STOVER: Rhonda Stover, FDA.

19 DR. POMERANTZ: Roger Pomerantz,  
20 virologist, infectious disease, Thomas Jefferson  
21 University, Philadelphia.

22 DR. LIPSKY: Jim Lipsky, clinical  
23 pharmacology, Mayo Clinic, Rochester, Minnesota.

24 DR. HAMILTON: John Hamilton, infectious  
25 diseases, Duke University.

1 DR. SOON: Greg Soon, statistical  
2 reviewer, FDA.

3 DR. NGUYEN: My name is Tan Nguyen. I'm  
4 the medical reviewer at FDA.

5 DR. FLEISCHER: Russ Fleischer, clinical  
6 reviewer, Division of Antiviral Drug Products.

7 DR. BEHRMAN: Rachel Behrman, team leader,  
8 Division of Antiviral Drug Products.

9 DR. MURPHY: Dianne Murphy, Office  
10 Director, FDA.

11 DR. JOLSON: Heidi Jolson, Division  
12 Director, Division of Antiviral Drug Products.

13 CHAIRMAN HAMMER: Thank you. I would also  
14 like to officially welcome Doctors Pomerantz and  
15 Hamilton as members of the committee, and I'd like to  
16 turn now to Dr. Jolson and welcome here as the new  
17 Director of the Division. It's our first official  
18 meeting together. Thank you.

19 DR. JOLSON: Well, good morning. Good  
20 morning and welcome to the first day of what we're  
21 certain will be an interesting and productive three-  
22 day meeting.

23 I'd like to first welcome back our regular  
24 committee members, and I'd like to especially welcome  
25 those of you who are joining our committee for the

1 first time today. I would also like to officially  
2 welcome Dr. Dianne Murphy, who many of you know from  
3 her participation on this committee. Dianne is  
4 sitting on the FDA side of the table, since recently  
5 rejoining FDA as our Office Director.

6 As you're aware, today we will be  
7 considering for traditional approval the New Drug  
8 Application for the combination use of interferon  
9 alfa-2b with oral ribavirin for the treatment of  
10 patients with chronic hepatitis C and compensated  
11 liver disease who have relapsed after prior alfa  
12 interferon therapy.

13 This is an interesting application in  
14 several respects and, importantly, provides this  
15 committee with its first opportunity to discuss an  
16 application for treatment of viral hepatitis.

17 In the next few moments, I'd like to  
18 provide a little stage setting, first by clarifying  
19 the regulatory status of these products and, second,  
20 by providing a brief context for the clinical  
21 development program that you'll hear about today.

22 From the regulatory perspective, this  
23 application is somewhat unusual, because it contains  
24 both a biologic, interferon, and a drug, ribavirin;  
25 and the two types of products, interestingly, are

1 regulated by two different centers in FDA.

2 Therefore, the FDA review of this  
3 application which you'll hear today represents the  
4 collaborative effort between reviewers in both  
5 centers, and I'd like to take this opportunity to  
6 thank our colleagues in the Center for Biologics  
7 Evaluation and Research for their help.

8 As you are aware, alfa interferon was  
9 licensed for the treatment of hepatitis C, or what was  
10 at the time referred to as non A non B hepatitis in  
11 1991. Its licensure was based on improvement in serum  
12 ALT levels and liver biopsy.

13 Ribavirin is also an approved product,  
14 although under different sponsorship than the  
15 applicant today. Ribavirin's approved formulation is  
16 a lyophilized powder for aerosolized short term use in  
17 infants and young children with respiratory syncytial  
18 virus infection.

19 It is noteworthy also that many varied  
20 potential uses of oral and intravenous ribavirin have  
21 been investigated as a possible treatment for a wide  
22 variety of viral illnesses over the years.

23 Therefore, while individually we  
24 understand quite a bit about the safety and efficacy  
25 profiles of both interferon and ribavirin, their use

1 together in combination for the treatment of hepatitis  
2 C in treatment experienced patients raises many new  
3 and interesting clinical issues.

4 Almost four years ago we asked this  
5 committee for guidance on the clinical development of  
6 new therapies for hepatitis B and C. We well  
7 recognize that demonstration of clinical benefit with  
8 these products would be problematic, because of the  
9 long latency period before long term sequelae such as  
10 cirrhosis and hepatocellular cancer would appear in  
11 chronically infected individuals.

12 You will hear presented today the results  
13 of two randomized controlled clinical trials in  
14 hepatitis C patients who have relapsed following  
15 previous therapy with alfa interferon alone.

16 The endpoint assessments in this  
17 development program are consistent with the spirit of  
18 your guidance, which was the need to demonstrate a  
19 sustained response to treatment after cessation of  
20 therapy and the need to assess both virologic and  
21 histologic improvement.

22 Nonetheless, we are still left with  
23 several important questions about the role of a short  
24 term therapeutic intervention with well characterized  
25 toxicities for the treatment of a chronic lifelong

1 disease.

2 We will look forward to your discussion  
3 and perspective on this question and other issues that  
4 we will raise following this morning's presentations.  
5 Thank you.

6 CHAIRMAN HAMMER: Thank you. I'd like to  
7 turn now to the sponsor presentation from Schering  
8 Corporation, to be led off by Dr. Penelope Giles.

9 DR. GILES: Good morning. My name is  
10 Penny Giles. I'm in regulatory affairs with Schering  
11 Corporation.

12 We're here today to talk about the data  
13 that we have to support the use of combination Intron  
14 A, a biologic, as Dr. Jolson mentioned, with Rebetol,  
15 a new drug, for the treatment of chronic hepatitis C  
16 in patients who have previously relapsed.

17 This latest development is the latest  
18 project for Schering-Plough and represents Schering's  
19 ongoing commitment to hepatitis research. Rebetol was  
20 licensed by Schering in the summer of 1995, and  
21 Schering has been solely responsible for its clinical  
22 development.

23 The only currently approved, recognized,  
24 safe and efficacious treatments for chronic hepatitis  
25 C are the interferon alfas. The interferon alfas,

1 however, do have a relatively high relapse rate. Even  
2 with longer treatment duration, which Schering has  
3 demonstrated doubles the response of treatment, as  
4 well as a sustained response still has a high relapse  
5 rate.

6 We think that the combination here with  
7 the data we'll go through today will show you  
8 significant improvement in the treatment of chronic  
9 hepatitis C, and the data that we hope that you will  
10 agree supports the following indication, that the  
11 combination of Intron with Rebetol is indicated for  
12 the treatment of chronic hepatitis C in patients 18  
13 years or older with compensated liver disease who have  
14 relapsed following alfa interferon therapy.

15 We have quite a bit of data to go through  
16 today. So we only have two speakers, and with that  
17 I'd like to turn the podium over to Dr. Albrecht, who  
18 will review with you the clinical efficacy and safety  
19 information we have on this combination.

20 DR. ALBRECHT: Thank you, Dr. Giles.

21 Ladies and gentlemen of the Advisory  
22 Board, my name is Janice Albrecht. I'm the Director  
23 of the Hepatology program at Schering-Plough Research  
24 Institute.

25 Today it is my pleasure to share with you

1 the results of two controlled clinical trials  
2 evaluating the safety and efficacy of Intron A in  
3 combination with Rebetol for the treatment of chronic  
4 hepatitis C in relapsed patients.

5 During the past decade, hepatitis C  
6 infection has come to be recognized as a major health  
7 care problem worldwide. It is estimated there are  
8 approximately 100 million patients infected worldwide.  
9 Of these, about 4 million are Americans.

10 Of the infected patients, about 70 percent  
11 have elevated ALTs with hepatic inflammation. As Dr.  
12 Jolson indicated, chronic hepatitis C is a silent,  
13 slowly progressive disease that may take decades to  
14 manifest its clinical symptoms. However, it is a  
15 serious disease in that approximately 20-50 percent of  
16 patients develop cirrhosis with the possibility of  
17 progression to liver failure and hepatocellular  
18 carcinoma.

19 I think the seriousness of this disease is  
20 illustrated by the fact that in the United States the  
21 most common reason for liver transplantation is  
22 chronic hepatitis C.

23 The CDC estimates that approximately  
24 12,000 liver deaths occur each year which are related  
25 to chronic hepatitis C. They have projected by the

1 year 2010 that this number will triple.

2 So we really are dealing with a very  
3 serious disease that infects a large number of  
4 patients.

5 As Dr. Jolson indicated, the ultimate goal  
6 with a chronic disease is to halt disease progression  
7 and decrease morbidity and mortality. With  
8 therapeutics, we are hampered by the fact that we  
9 cannot wait for 20 years to find the endpoint.

10 Therefore, based on the recommendation of  
11 this committee several years ago and the scientific  
12 field, we have moved towards a combined endpoint of  
13 sustained loss of HCV RNA at least six months  
14 following the end of therapy as one of the first  
15 markers.

16 It's important that serum HCV RNA be  
17 measured using a sensitive assay and one that is  
18 reliable. At the current time, there is no licensed  
19 assay. However, there are available reliable,  
20 sensitive reverse transcription PCR assays which have  
21 been used in these trials, and I will discuss.

22 The second part of the equation is the  
23 improvement in hepatic inflammation. This information  
24 is obtained by looking at the liver biopsy pre-therapy  
25 and post-therapy and equating the improvement with

1 relation to the loss of HCV RNA.

2 In the last year, some very interesting  
3 data has been evolving. As Dr. Jolson indicated, the  
4 use of Intron and the alfa interferons for the  
5 treatment of chronic hepatitis C has been in place for  
6 close to 12 years, the initial studies being done by  
7 Dr. Hoofnagel at the NIH.

8 What we are seeing in the retrospective  
9 evaluation of these patients is that patients who were  
10 PCR negative at six months following the end of  
11 therapy remain so through the follow-up period, some  
12 as long as 12 years, and that with the continued loss  
13 of HCV RNA actually do show liver biopsies in the long  
14 term follow-up that are basically normal.

15 In none of the patients who remain PCR  
16 positive, to my knowledge, in the literature books  
17 from Patrick Marcellin's group in Paris and now from  
18 Dr. Hoofnagel has there been disease progression.

19 So I think we have identified, if you  
20 will, a surrogate marker that is the best we can do at  
21 this point in time, and appears to be very much  
22 related to long term outcome.

23 As Dr. Jolson mentioned, Intron A has been  
24 licensed for the treatment of chronic hepatitis C  
25 since 1991. The dosage for which it is licensed is 3

1 million units three times a week for 18-24 months.

2 The original license was for six months of  
3 treatment. We found with subsequent studies that  
4 longer durations of therapy resulted in a better  
5 response rate. The current license specifies that 24  
6 percent of patients have sustained normalization of  
7 ALT six months post-treatment.

8 These studies were conducted in the era  
9 prior to the availability of RT PCR. One can estimate  
10 that probably 50-75 percent of patients with sustained  
11 normal ALT probably are PCR positive.

12 As Dr. Jolson mentioned, ribavirin is a  
13 nucleoside analog that is active against RNA viruses  
14 and is used in the aerosol form for RSV.  
15 Interestingly enough, when monotherapy studies were  
16 conducted for the treatment of chronic hepatitis C, it  
17 was found that, although ribavirin normalized ALT in  
18 a proportion of patients, it did not affect the virus  
19 load. That is, HCV RNA did not decrease.

20 So interestingly enough, this drug which  
21 is known to be an antiviral was ineffective as  
22 monotherapy for chronic hepatitis C.

23 In the early 1990s in Europe, people began  
24 to combine ribavirin and Intron A and some of the  
25 other alfa interferons to determine if the combination

1 would have an effect on chronic hepatitis C. What we  
2 found was that in small numbers of patients, both  
3 those that were naive to treatment and relapsed  
4 patients, that you could significantly increase the  
5 sustained response rate six months following the end  
6 of treatment looking at the loss of HCV RNA.

7 In fact, we saw a two to tenfold increase  
8 in these very early pilot studies. But as with all  
9 pilot studies, small numbers do not tell the whole  
10 story.

11 Schering-Plough then conducted a Phase II  
12 study to confirm these results. We did this in naive  
13 patients. There were 50 patients in each treatment  
14 group. One group received Intron A/Rebetol 3 million  
15 units three times a week, the Rebetol being  
16 administered 1,000-1200mg with treatment for six  
17 months.

18 This was compared to an Intron A alone  
19 control that had a placebo. What we found in that  
20 study was using loss of HCV RNA measured at six months  
21 following the end of treatment, that the response rate  
22 in the combination group was 42 percent as compared to  
23 the Intron alone at 20 percent.

24 I will comment for those of you that are  
25 familiar with chronic hepatitis C studies that the

1 Intron control looks high in this study, and this is  
2 probably because a majority of these patients had  
3 Types 2 and 3.

4 I would now like to summarize for you the  
5 Schering-Plough Research Institute clinical program.  
6 We basically have looked at two populations, relapsed  
7 patients. Those are patients who have previously  
8 responded to alfa interferon with a normalization of  
9 ALT at the end of therapy, and then relapsed with  
10 elevated ALT following discontinuation of therapy.

11 We have conducted two studies which are  
12 the basis of our discussion today. The doses used in  
13 all of our studies are 3 million units three times a  
14 week Intron A administered subcutaneously, in  
15 combination with Rebetol 1,000-1200mg per day  
16 administered orally in divided doses.

17 Patients less than 75 kilograms received  
18 1,000mg and greater than or equal to 75 kilograms  
19 received 1200.

20 We also have ongoing studies in naive  
21 patients, two large studies in a total of 1744  
22 patients. In these studies we are also examining the  
23 effect of duration of therapy, 24 weeks versus 48  
24 weeks.

25 As I mentioned previously, with the alfa

1 interferon monotherapy and Intron A, longer duration  
2 of therapy has been shown to be more effective.

3 We have initiated also a study to optimize  
4 the dose of Rebetol. As you can see on the bottom,  
5 this study is examining four, six, 800 and 1000-1200mg  
6 of Rebetol in comparison with placebo.

7 The objective of this study is to  
8 determine if we can maintain the antiviral effect that  
9 we have seen with the combination at 1000-1200mg of  
10 Rebetol with a lower dose that may have a less -- or  
11 may have a better safety profile.

12 At the time we initiated the  
13 Intron/Rebetol, there was significant interest in  
14 having an expanded access program, and we had many  
15 requests from the hepatology community to conduct  
16 studies and have access to the drug.

17 What we decided to do, in cooperation with  
18 the FDA, was to initiate treatment protocols in the  
19 United States, and then we also initiated investigator  
20 studies in the international arena. We specified in  
21 these protocols that the patient population be the  
22 same one that we used in our registration trial; that  
23 is, patients with compensated liver disease, with or  
24 without previous interferon.

25 So, basically, we were allowing patients

1 that were very much like our registration protocol  
2 patients, naive patients, relapsed patients and, in  
3 some cases, patients that failed to respond to  
4 previous therapy.

5 We also required in these protocols that  
6 they use the same inclusion/exclusion criteria that we  
7 used in the registration protocols, and that the  
8 patient visit schedule be the same; because we were  
9 very concerned that, in an expanded access program,  
10 that adequate safety monitoring be part of the  
11 program.

12 To date, we have provided Rebetol for use  
13 in combination with Intron A for approximately 25,000  
14 patients. In the United States treatment protocol,  
15 the number is about 5,000, in the international  
16 investigator initiated studies, about 20,000.

17 I would now like to return to the -- I  
18 would like to turn to the results of the two pivotal  
19 clinical trials using Intron/Rebetol for the therapy  
20 of patients who have relapsed following interferon  
21 therapy.

22 There were two identical studies  
23 conducted. The protocols are exactly the same. One  
24 was conducted in the United States and was a multi-  
25 center study. The other one was conducted in Europe,

1 Canada, Israel and Australia.

2 These studies, as we previously mentioned,  
3 examined retreatment of chronic hepatitis C patients  
4 who had responded to interferon therapy but relapsed  
5 following the cessation of therapy.

6 Patients eligible to participate in the  
7 study were adults with compensated liver disease,  
8 documented chronic hepatitis C, and with a liver  
9 biopsy prior to the initiation of therapy. They were  
10 required to have previously responded to interferon  
11 therapy with relapse following the cessation of  
12 therapy.

13 Therapy -- Previous therapy allowed was  
14 one to two courses of Intron A, Roferon A or  
15 Wellferon. These drugs were selected, because Roferon  
16 and Intron were licensed in the United States, and  
17 Wellferon was licensed in the international arena.

18 Dosages which the patients could have  
19 received were 3-6 million units every other day or  
20 TIW. The minimum total duration of therapy was 20  
21 weeks to a maximum duration of 18 months.

22 Response was characterized in these  
23 patients as normalization at end of treatment --  
24 excuse me, normalization of ALT at end of therapy with  
25 relapse within one year. Relapse was characterized as

1 elevation of ALT.

2 The reason that we did not use a virologic  
3 endpoint in these studies is these patients were  
4 gathered from the community, and at that point in  
5 time, which was about two years ago, virologic testing  
6 was not readily available.

7 Patients were excluded from the study if  
8 they had liver disease of an etiology other than  
9 chronic hepatitis C, co-infection with hepatitis C or  
10 HIV. A particularly important exclusion criteria  
11 which is more detailed in the protocol was the  
12 exclusion of patients for systemic disease that was  
13 significant.

14 We defined significant systemic disease as  
15 any disease that would interfere with the evaluation  
16 of the experimental regimens or that the experimental  
17 regimens administered to such a patient would endanger  
18 the patient. Basically, we didn't want any patient  
19 that would be hurt by the experimental regimens.

20 Ribavirin is associated with hemolysis,  
21 and we'll talk about this a little later. Therefore,  
22 we were particularly careful about patients with  
23 cardiac disease, underlying cardiac disease, and the  
24 protocol specified that any patient with severe  
25 disease or unstable disease was to be excluded from

1 the protocol.

2 In addition, any patient in which a  
3 decrease in hemoglobin might cause an exacerbation of  
4 their disease or a serious adverse event was excluded  
5 from the protocol. So, basically, I think we need to  
6 say we were very careful about the patients with  
7 cardiac disease that we let in these studies.

8 Psychiatric adverse events have been  
9 associated with the alfa interferons. Therefore, we  
10 were careful about allowing patients with underlying  
11 psychiatric illness, in particular depression, in  
12 these studies. Patients who had a history of severe  
13 depression or had severe depression when they were  
14 evaluated for the study were excluded.

15 We also looked at hematologic parameters  
16 to assure that the patients coming into the study were  
17 adequately -- had adequate levels relative to the  
18 toxicities we anticipated to see with both ribavirin  
19 and Intron A.

20 As we will discuss, ribavirin is  
21 associated with hemolysis. Therefore, minimum  
22 hemoglobin levels were: Females, greater than 12  
23 grams per deciliter; and males, greater than 13 grams  
24 per deciliter. I should say equal to.

25 We know that decreases in WBC, neutrophils

1 and platelets occur with Intron A. Therefore, we had  
2 minimum criteria for entry to the study for these  
3 parameters.

4           Particularly important and very carefully  
5 monitored in these studies is the ability of a patient  
6 to practice adequate contraception. Ribavirin is  
7 mutagenic and teratogenic in animals. Therefore, we  
8 required that both males and females and the partners  
9 of females practice contraception during the treatment  
10 period and throughout the follow-up period.

11           The decision to require contraception  
12 during the follow-up was based on 15 half-lives of  
13 ribavirin.

14           I would now like to turn to the study  
15 design for these relapse trials. This is a rather  
16 complicated slide, but I will try to walk through it  
17 slowly.

18           Patients entered the screening phase to  
19 have their eligibility to enter the study determined.  
20 When patients were determined to be eligible, they  
21 were randomized using a central randomization  
22 procedure to a 24-week treatment phase. They were  
23 randomized to receive Intron A plus Rebetol or Intron  
24 A with a matching placebo.

25           Intron A was administered, 3 million

1 units, three times a week, administered  
2 subcutaneously. If the patient was randomized to  
3 receive Rebeto1, the patient received 1000-1200mg per  
4 day, given orally in divided doses, based on the  
5 patient's weight.

6 Patients randomized to receive Intron  
7 A/placebo received Intron A 3 million units, three  
8 times a week, administered subcutaneously, and a  
9 matching placebo to the Rebeto1 administered using the  
10 same dose schedule.

11 When the patient completed the 24 weeks of  
12 treatment, they moved into a follow-up phase of 24  
13 weeks. The total duration of the study was 48 weeks.  
14 At the end of the study, the patient was invited to  
15 enter a five-year follow-up protocol. All patients,  
16 whether responders or nonresponders, were invited to  
17 enter the protocol.

18 Biochemical, hematological and clinical  
19 assessments were performed at baseline, one week, two  
20 weeks, four weeks, six weeks, and eight weeks during  
21 the therapy, and then every four weeks for the  
22 remainder of the therapy to the 24 weeks.

23 During the follow-up period, patients were  
24 evaluated at week four, week 12 and week 24. A liver  
25 biopsy was obtained within six months prior to entry

1 to the study and again at 24 weeks following the end  
2 of therapy.

3 Serum for HCV RNA assessment by RTC PCR  
4 was obtained prior to entry to the study, at week four  
5 of treatment, week 12 of treatment, and week 24 of  
6 treatment. It was also obtained at four, 12 and 24  
7 weeks following the end of therapy.

8 The primary efficacy endpoint of the study  
9 was assessed at 24 weeks following end of therapy. It  
10 is defined as overall response. It is a composite  
11 endpoint incorporating the two parameters that we  
12 believe reflect response to treatment.

13 The first is loss of detectable HCV RNA  
14 measured by RT PCR. The second is improvement in  
15 hepatic inflammation.

16 The improvement in hepatic inflammation  
17 was measured using a Knodell histologic activity index  
18 of which the first three categories were used to  
19 create an inflammation score. Response was defined as  
20 a decrease greater than equal to two in the score.

21 In the next slide I will show you the  
22 basic outline of the Knodell histologic activity  
23 index. This score allows the grading of liver  
24 injury. There are four parts to the score.

25 The first three parts of the score grade

1 necroinflammatory activity at different levels within  
2 the biopsy, and the fourth part of the score is used  
3 to stage hepatic fibrosis.

4           The first three parts of the score were  
5 combined, as I indicated, to create an inflammation  
6 score, and it was the change in this inflammation  
7 score from pre-treatment to post-treatment biopsy that  
8 was used to assess improvement in inflammation.

9           All of the liver biopsies for this study  
10 were read by a single pathologist. Our pathologist  
11 was blinded as to the patient identification, the  
12 timing of the liver biopsy, pre-treatment versus post-  
13 treatment, the outcome of the patient's treatment, and  
14 the patient's treatment assignment. So the  
15 pathologist who read our liver biopsies did so  
16 completely randomly.

17           I would now like to turn to the patient  
18 demographics for this study. I think the most  
19 important thing to note about this slide is that the  
20 demographics for these patients, both within the  
21 trials, within the two individual trials -- the U.S.  
22 study is shown here, 153 patients, and the  
23 international trial 192 patients -- were similar  
24 within studies and between studies.

25           The majority of our patients were middle

1 aged males who were Caucasian. The Americans were  
2 slightly heavier than the Europeans -- not just  
3 slightly heavier, quite a bit heavier. The source of  
4 HCV infection was parenteral in about 50 percent of  
5 the patients in the U.S. studies and about 35 percent  
6 of the patients internationally.

7 The other sources of infection were  
8 divided equally between transfusion and sporadic.  
9 Sporadic is really classified as unknown.

10 Disease characteristics were also balanced  
11 within each of the studies, as well as between the  
12 studies. We had reasonable balance all the way  
13 through these protocols. The majority of the patients  
14 were genotype 1.

15 As you will notice, the genotype 1 ranged  
16 from 55 to 60 percent, and those of you familiar with  
17 hepatitis C in this country and Europe will say that  
18 seems a little bit low. We must remember that these  
19 patients have been previously treated and, indeed,  
20 genotype 1 is a predictor of nonresponse with  
21 interferon monotherapy.

22 The majority of the patients had HCV RNA  
23 levels that were greater than 2 million copies per  
24 milliliter on entry to the study. All patients had  
25 elevated ALT, as required by the protocol, and they

1 ranged between 2.3 and 2.7 times the upper limit of  
2 normal.

3 The Knodell HHI inflammation score, you  
4 will notice, was about seven, which is relatively mild  
5 diseased, but is consistent with what you see in  
6 chronic hepatitis patients. There was very little  
7 cirrhosis in this study. You will note that, in fact,  
8 there was virtually no cirrhosis in this study.

9 That, again, is not particularly  
10 surprising in that patients with cirrhosis do not in  
11 general respond well to interferon monotherapy. The  
12 majority of the patients had been treated with one  
13 course of Intron A for a duration of six to nine  
14 months.

15 I would now like to turn to the efficacy  
16 results for these two trials. We used an analysis  
17 that included all treated patients. That is any  
18 patient who received at least one dose of the study  
19 medication.

20 As I mentioned a moment ago, we had two  
21 efficacy endpoints. I would like to first cover the  
22 individual endpoints and then move on to the composite  
23 score.

24 In the next slide is the response rate  
25 based on loss of serum HCV RNA at the end of follow-

1 up, 24 weeks following the end of treatment. The  
2 studies are shown individually. The United States is  
3 on the left, the international study on the right.

4 On the y axis is the percent of patients  
5 with loss of HCV RNA. In yellow, the Intron/Rebetol,  
6 and in blue -- but it's so small you can barely see it  
7 -- the Intron/placebo.

8 I think what is very important to note  
9 about these slides is that, as we go through the  
10 efficacy, you will see that the results in the two  
11 studies conducted in two geographical locations are  
12 almost identical.

13 In the United States, the Intron/Rebetol  
14 group, 44.2 percent of the patients had sustained loss  
15 of HCV RNA, and in the Intron/placebo group 3.9  
16 percent. Very similar data in the international  
17 study, 52.1 percent versus 5.2 percent. This  
18 represents a tenfold increase in the efficacy with the  
19 combination therapy. Both studies are statistically  
20 significant at p less than .001.

21 There were 277 patients in these studies  
22 who had paired liver biopsies -- that is, both pre-  
23 and post. This is about 80 percent of the patients,  
24 which actually is a fairly good recover rate for  
25 paired liver biopsies.

1           The data in this slide with histologic  
2 improvement is based on those patients which have  
3 paired liver biopsies. As in the previous slide, the  
4 studies are shown individually, the United States  
5 versus international, and the colors remain the same  
6 for the treatment group, yellow for Intron A/Rebetol,  
7 and blue for Intron A/Placebo.

8           On the lefthand side are the percent of  
9 patients with improvement in liver biopsy, which I  
10 will remind you is the combination of the first three  
11 categories of the Knodell HAI, the inflammation score;  
12 a decrease of greater than or equal to 2 was  
13 considered improvement.

14           In the U.S. study 62.2 percent of the  
15 patients who received the combination improved,  
16 compared with 42.2 percent of the Intron A patients.  
17 The results were similar in the international studies,  
18 63.8 percent versus 40.5 percent. Both of these are  
19 statistically significant in favor of Intron  
20 A/Rebetol.

21           I think what is important to mention is  
22 this represents all treated patients. When you look  
23 at histologic improvement relative to response at the  
24 end of 24 weeks of treatment, as measured by loss of  
25 HCV RNA, we find that the patients who responded 83

1 percent had improvement in liver biopsy. So 83  
2 percent of the patients that were PCR negative also  
3 had an improved liver biopsy.

4 I would actually like to show you in the  
5 next slide the magnitude of this improvement. This  
6 slide shows mean change from baseline in Knodell HAI.  
7 On the lefthand side we've moved the -- where the  
8 studies usually are is the U.S. study and the  
9 international study. Again, this represents patients  
10 with paired biopsies.

11 Responders are those patients who were PCR  
12 negative at the 24 week follow-up. Nonresponders are  
13 those patients who either were negative at the end of  
14 treatment and relapsed or never responded.

15 As you will notice, the mean change from  
16 baseline in the responders was about four. I would  
17 remind you that the baseline score in these people was  
18 just slightly less than seven. So this is a very  
19 large increase.

20 I would also like to point out that, no  
21 matter how you got to being PCR negative, whether it  
22 be by Intron/Rebetol or Intron/placebo, you had a  
23 significant improvement in your hepatic inflammation.  
24 However, I think it's also important to notice that  
25 the proportion of patients with this improvement is

1 tenfold greater in the combination. In the  
2 nonresponders, there was some minimal improvement in  
3 the mean change from baseline.

4 I would now like to move to the composite  
5 endpoint, the overall response, which combines the  
6 virology and the histologic improvement. When we  
7 designed the protocol, we recognized it was going to  
8 be very difficult, if not impossible, to obtain 100  
9 percent of paired biopsies. As I indicated, we did  
10 obtain 80 percent.

11 Therefore, there were two protocol defined  
12 analyses. One was in patients with paired biopsies.  
13 That is the subpopulation in which both pre- and post  
14 liver biopsies were available.

15 We also performed a maximum likelihood  
16 estimate, which took into account the association  
17 between loss of HCV RNA and histologic improvement.  
18 When we look at these two analyses, we find that they  
19 have very similar results.

20 In the U.S. study in the Intron A/Rebetol  
21 group, 36.5 percent of the patients had improvement  
22 with the MLE, and 41 percent with paired biopsies,  
23 compared to the Intron A/placebo group, 2.7 by the MLE  
24 and 3.1 when we look at patients with paired biopsies.

25 The international data is very similar,

1 42.7 percent with the MLE in the combination, compared  
2 with 50 percent and 5.2 versus 5.4 for the Intron  
3 A/placebo.

4 We also performed a nonprotocol defined  
5 analysis, and that is an analysis in which we treated  
6 all missing biopsies as failure. From a clinical  
7 perspective, this analysis underestimates the true  
8 response rate, in that we are saying that all patients  
9 who were missing their biopsies, even if they were HCV  
10 RNA negative, were failures, when we know that 83  
11 percent of the patients who are PCR negative do have  
12 histologic improvement.

13 In this analysis we see that 32 percent  
14 versus 2.6 percent in the U.S. study in favor of the  
15 combination, 40.6 percent versus 4.2 percent in favor  
16 of the combination in the international study. So  
17 even by this analysis, we continue to see the tenfold  
18 increment in efficacy with the combination. All these  
19 analyses are statistically significant at the p less  
20 than .001.

21 On entry to the study we stratified  
22 patients by those factors which have been associated  
23 with -- or as a negative predictor for response with  
24 alfa interferon monotherapy. They were stratified  
25 based on serum HCV RNA less than or equal to 2 million

1 or greater than 2 million copies per ml. They were  
2 also stratified by HCV genotype, type 1 versus non-1,  
3 and cirrhosis.

4 Logistic regression analysis on this data  
5 showed that both HCV RNA and genotype were important  
6 predictors of response. As I showed you early in the  
7 demographics, there were not enough patients with  
8 cirrhosis to assess.

9 This is a very interesting slide. In this  
10 slide we have combined genotype with virus load using  
11 the stratification variables. This slide represents  
12 the combined data for the two studies in order to show  
13 the data.

14 As in previous slides, the Intron/Rebetol  
15 group is in yellow, and the Intron A/placebo group is  
16 in blue. On the lefthand side are the percent of  
17 patients with loss of HCV RNA 24 weeks following the  
18 end of therapy or end of follow-up.

19 Across the bottom we have arrayed, first  
20 by genotype non-1, and then by genotype 1, and then  
21 subset to that the baseline virus load within each  
22 genotype.

23 I think what is very important to notice  
24 as a first indicator and what we would expect is that  
25 the Intron/Rebetol combination is substantially more

1 effective than Intron alone in all genotypes and all  
2 virus loads.

3           Within genotypes and virus loads, we find  
4 that those patients with non-1 genotype and low virus  
5 loads have a very high proportion of response. It is  
6 almost a stairstep effect. Patients with 1 genotypes  
7 and higher virus loads have a very good response but  
8 lower than those with low virus loads.

9           I think what is very important is in the  
10 genotype 1 patients, who we consider the most  
11 difficult to treat, that with low virus load we had 44  
12 percent of response, and in those very difficult to  
13 treat patients, genotype 1 greater than 2 million,  
14 there is a 24 percent response.

15           As you can see, the response rates -- the  
16 distribution are similar for Intron A/placebo, but  
17 very much lower. In fact, in genotype 1 with high  
18 virus load no patient responded.

19           In conclusion, Intron A Rebetol therapy  
20 results in significant efficacy when measured by loss  
21 of HCV RNA at the end of follow-up and in overall  
22 response when we combine histologic improvement and  
23 loss of HCV RNA.

24           I think particularly important is the fact  
25 that the benefit of the combination is maintained,

1       irrespective of the baseline HCV level and the HCV  
2       genotype.

3               I would now like to turn to the evaluation  
4       of safety of these two compounds, the Phase III  
5       controlled clinical trials and some conclusions based  
6       on the expanded access.

7               The patient population that we have  
8       available for safety is shown on this slide.  
9       Intron/Rebetol treatment was conducted in 173 patients  
10      in the relapse trials. In order to provide a more  
11      comprehensive picture of the safe, we performed an  
12      interim analysis at 24 weeks for safety in the ongoing  
13      naive studies.

14              We were, thus, able to evaluate safety for  
15      1,010 patients in the naive population, allowing us to  
16      have a safety database of 1183 patients. Supportive  
17      data is also available from the expanded access  
18      program.

19              In the briefing book we provided you with  
20      a list of the complete adverse event profile for those  
21      adverse events which were observed in greater than or  
22      equal to five percent of the patients. Therefore, in  
23      my presentation I would like to focus upon particular  
24      issues that are of clinical interest.

25              First, I would like to summarize the

1 Intron A safety profile. Intron A has been licensed  
2 since 1991 for the treatment of chronic hepatitis C,  
3 and is well characterized. Virtually all patients  
4 have flue-like symptoms, fevers, chills, myalgia,  
5 which diminish with continued treatment.

6 Fatigue, malaise and anorexia are common.  
7 Alopecia is a problem. This is hair thinning rather  
8 than hair loss, and occurs in about 25 percent of the  
9 patients. Psychiatric side effects occur in about 20  
10 percent of the patients, primarily depression.

11 As I mentioned previously, decreases in  
12 hematologic parameters, including WBC, neutrophils and  
13 platelets are characteristic of Intron A.

14 In contrast, the side effect profile for  
15 ribavirin, which was derived from the monotherapy  
16 studies, is different. Hemolysis is the defining  
17 toxicity.

18 It is postulated that the myelosis is due  
19 to the fact that ribavirin accumulates in the red cell  
20 as a triphosphate and, because the red cell is a non-  
21 nucleated cell, it is not metabolized, and thus it  
22 results in hemolysis. Rash, pruritus and  
23 gastrointestinal complaints were also reported in the  
24 monotherapy studies.

25 When we initiated the clinical protocol

1 for these combination studies, we had a small amount  
2 of data from the pilot studies, and the data from the  
3 pilot studies suggested that what we would see in the  
4 clinical protocol was a combination of these two side  
5 effects profiles without any exacerbation between the  
6 two, and this was indeed what we found.

7 The basis for dose discontinuation and  
8 dose reduction are shown in the next slide, as used in  
9 the clinical protocols, and will give you a  
10 perspective as to how and why patients were dose  
11 reduced or discontinued.

12 For the hematologic parameters,  
13 hemoglobin, WBC, neutrophil and platelet count, we  
14 reduced dose based on the observed toxicity. For  
15 example, with hemoglobin we did not expect hemoglobin  
16 problems with Intron A. Therefore, Rebetol or placebo  
17 was reduced to 600mg per day if the hemoglobin dropped  
18 to less than six grams per deciliter, and both drugs  
19 were discontinued if hemoglobin dropped to less than  
20 8.5 grams per deciliter.

21 WBC, neutrophil count and platelet count  
22 are toxicities associated with Intron A. Therefore,  
23 we used a strategy that said, if these drop in the  
24 absence of hemoglobin, that Intron A would be reduced  
25 to 1.5 million units three times a week, based on

1 these parameters, and if we continued WBC, neutrophil  
2 or platelet count problems, both drugs would be  
3 reduced.

4 For side effects that required dose  
5 reduction other than these specific hematologic  
6 parameters, both drugs were reduced, because we were  
7 unsure which drug might be causing the toxicity. In  
8 the event of side effects that actually required  
9 discontinuation of therapy, we also required that both  
10 drugs be discontinued.

11 So when we look at the safety, we need to  
12 look at it in the light of how we dose modified and  
13 how we discontinued therapy.

14 I'd like to turn now to the pattern of  
15 hemoglobin and reticulocyte counts during and post-  
16 treatment. This is a rather complicated slide, but it  
17 contains a lot of data.

18 In the left panel is the data from the  
19 relapse study, the 345 patients treated in two pivotal  
20 trials. In the right panel for comparison is the data  
21 from the naive studies, 1,744 patients of whom 1,010  
22 are Intron/ribavirin.

23 You will note that we only have 24 weeks  
24 of treatment in these studies. In the left panel --  
25 I think it might be a little hard to see -- this is

1 hemoglobin in grams per deciliter. ON the righthand  
2 side of the right y axis is reticulocyte count  
3 percent. Across the bottom is the treatment period,  
4 24 weeks of treatment, 24 weeks of follow-up.

5 Introl/Rebetol hemoglobin are the yellow  
6 closed circles. Introl/Rebetol reticulocytes are the  
7 open yellow circles. Intron alone hemoglobin are the  
8 blue filled squares. Reticulocytes are the open  
9 squares.

10 In the Intron/Rebetol group, the  
11 hemoglobin level decreased from 14.4 to about 12.2 at  
12 week 12 -- or excuse me, at week 4. Thereby, it's  
13 stabilized for the remainder of therapy, and within  
14 four weeks following the end of therapy it returned to  
15 baseline.

16 We saw a brisk reticulocytosis that  
17 started about the same time as the hemoglobin began to  
18 drop, continued throughout therapy, and returned to  
19 baseline within the four weeks following the end of  
20 therapy.

21 Approximately ten percent of patients in  
22 the Introl/Rebetol group had their hemoglobin drop to  
23 less than 10 grams per deciliter. This was controlled  
24 by dose modification, as I previously indicated, and  
25 no patient was discontinued from therapy with decrease

1 in hemoglobin as a primary reason.

2 There was only minimal drop in the Intron  
3 A monotherapy group. The drop was about .8 grams per  
4 deciliter. There was virtually -- There was really no  
5 increase in reticulocyte count, and this small  
6 decrease returned to baseline levels within four  
7 weeks, much as the Intron A/Rebetol group.

8 I think we can see from the panel in the  
9 naive patients that the response was very, very  
10 similar and gives us confidence that the data we see  
11 in the smaller population is consistent with that when  
12 we treat more patients.

13 As I indicated earlier, decreases in WBCs  
14 and neutrophils during and post-treatment can be a  
15 problem with Intron A. Therefore, it was extremely  
16 important that we look to see if the addition of  
17 Rebetol to the Intron A would increase the amount of  
18 drop that we see.

19 This slide is set up very much like the  
20 previous one. On the lefthand side are WBC neutrophil  
21 counts, absolute. Across the bottom is the treatment  
22 phase, the 24 weeks of therapy followed by the 24  
23 weeks of follow-up.

24 The yellow circles are the WBC  
25 Intron/Rebetol. The yellow open circles are the

1 neutrophil count. Blue represents Intron A/placebo.  
2 Again, the blue squares are the WBC. The blue open  
3 boxes are the neutrophils.

4 In the righthand panel again is the data  
5 from the naive trial using the same color coding.  
6 What we saw was what we had anticipated would happen.  
7 There was a decrease in WBC and neutrophils during  
8 essentially the first four weeks of therapy, reaching  
9 its nadir about four weeks, and then remaining  
10 basically stable to the end of therapy, with a return  
11 to baseline within four weeks following the end of  
12 therapy.

13 For the treatment period, the data that we  
14 see in the larger population is similar.

15 This slide shows the effect on platelets  
16 during and post-treatment. The slide is also set up  
17 as the previous one. The platelet count is on the y  
18 axis. The treatment duration and follow-up are across  
19 the bottom.

20 Intron A/Rebetol are the closed yellow  
21 circles, and Intron A/placebo the closed blue boxes.

22 Upon initiation of therapy with Intron  
23 alone, we saw a drop in platelets, again which  
24 stabilized by about week four, reaching its nadir and  
25 remains stable until the end of therapy, when it went

1 back to baseline levels.

2 Interestingly enough, in the  
3 Intron/Rebetol group there was very little drop in the  
4 platelets, and they remained stable throughout the  
5 course of therapy. This is probably due to the fact  
6 that the hemolysis was inducing a thrombocytosis.

7 I would now like to turn to the  
8 cardiovascular events that were observed during these  
9 trials and the psychiatric events. I think these are  
10 the areas that we're probably most interested in,  
11 because we were very concerned about patients with  
12 underlying cardiac disease who might enter the study,  
13 and we were also concerned about the potential for  
14 Intron A side effects with regard to psychiatric  
15 problems.

16 There are two sets of data shown here.  
17 The relapse study -- and in this data the  
18 international and the U.S. study are combined. So the  
19 Intron/Rebetol group is 173 patients. The  
20 Intron/placebo group is 172.

21 On the righthand side is the naive data,  
22 1010 patients in the Intron/Rebetol group, and 734 in  
23 the Intron A/placebo group.

24 I think the naive data serves to reinforce  
25 the kinds of things that we see in the relapse study,

1 because this is a larger population. On the lefthand  
2 side we have listed the most frequent side effects  
3 that occurred relative to cardiovascular events, and  
4 on the bottom part of the panel the causes for  
5 discontinuation.

6 Chest pain was the most frequently  
7 observed side effect, and the data is interesting in  
8 the fact that in the Intron A/placebo group the most  
9 frequent group -- the highest percentage of patients  
10 is in the Intron A/placebo. When you look at the  
11 Intron/Rebetol groups in both the relapse and the  
12 naive and the Intron A/placebo groups, they are fairly  
13 consistent.

14 So I think that it's difficult to make an  
15 assessment based on these small numbers of events as  
16 to whether there is an increase in chest pain.

17 In tachycardia we see there's a slightly  
18 higher percentage in the Intron/Rebetol group, 2.3  
19 percent, and 1.7 percent in the relapse and naive,  
20 compared to the placebo groups, .6 and .8.

21 In contrast, with hypertension we see a  
22 lower level of side effects in the Intron/Rebetol  
23 group and the relapse, and approximately equal numbers  
24 in the Intron A/placebo and Rebetol groups; and again  
25 you see the variance among these. These are small

1 numbers, and it does not appear that we have an excess  
2 of cardiac adverse events.

3 Again, with palpitation we see a lower  
4 level in the Intron relapse group, the Intron/Rebetol  
5 relapse group, and consistent numbers across the other  
6 three groups.

7 So I think we really feel that there is  
8 not an excess of cardiac events with Intron/Rebetol,  
9 and that the Intron/Rebetol and Intron/placebo groups  
10 look similar.

11 The bottom panel shows the reasons why  
12 patients were discontinued. There was one patient  
13 that was discontinued for bundle branch block, and  
14 indeed when we looked at this, this patient had had  
15 this previously to entry in a distant history.

16 We had one patient who had cardiac failure  
17 in the Intron/Rebetol group. Two patients were  
18 discontinued for chest pain in the Intron/Rebetol  
19 group in the naive study, and one patient in the  
20 Intron/placebo group.

21 We had one patient with tachycardia  
22 secondary to hyperthyroidism. As you may know,  
23 thyroid dysfunction can be associated with Intron  
24 treatment, and we had no patients discontinued in the  
25 naive patients.

1           So overall, we had one discontinuation in  
2 the Rebetol group, none in the Intron A/placebo group  
3 for the relapse, and equal numbers in the  
4 Intron/Rebetol group and placebo group in the larger  
5 patient populations.

6           The most frequent psychiatric side effects  
7 that we saw during treatment are shown here. Again,  
8 the slide is set up as the previous one. Number of  
9 patients at the top with percent, the relapse study,  
10 the naive studies and, for reference, the Intron A  
11 current labeling, which is 3 million units three times  
12 a week.

13           The most frequent side effects are shown  
14 on the left, and serious side effects are shown below  
15 that. The most frequent side effect that was observed  
16 in this study relative to psychiatric events was  
17 insomnia.

18           You can see that in the Intron/Rebetol  
19 groups compared to the placebo and the relapse study,  
20 they were very consistent, 20 and 23. However, in the  
21 larger population the Intron/Rebetol group had a  
22 higher incidence of insomnia than the placebo group.  
23 Across all of these studies, this was higher than has  
24 previously been reported in our earlier clinical  
25 trial.

1           Depression was the next most frequent side  
2 effect reported by the patients. IN the relapse  
3 studies there was a higher incidence in the  
4 Intron/Rebetol group, 16 percent versus 11 percent in  
5 the placebo. However, in the larger population the  
6 rates were almost identical, and were consistent with  
7 what has been shown in the labeling.

8           The reason for the smaller amount of  
9 depression in the relapse study is not known, but one  
10 could postulate that, since these patients have  
11 previously been treated with interferon, we may have  
12 excluded patients who were likely to experience  
13 psychiatric side effects.

14           Irritability also occurred in about 15  
15 percent of patients, and the numbers were consistent  
16 across all treatment groups in both studies and were  
17 fairly consistent with the current label.

18           We were, of course, all very worried about  
19 the serious psychiatric side effects such as suicidal  
20 ideation, suicide attempt and suicide itself. In  
21 these trials we had a small number of patients that  
22 had these events.

23           Suicidal ideation occurred in one patient  
24 in the Intron A/placebo group, five patients in the  
25 Intron A/Rebetol group in the naive study, and two

1 patients in the Intron A/placebo group. Because of  
2 the different n sizes in these two populations, you  
3 can see that the rate is similar in the Intron  
4 A/Rebetol and Intron A/placebo group in the naive  
5 patients.

6 We had one suicide attempt in the Intron  
7 A/Rebetol relapse study, and two suicide attempts in  
8 the Intron A/Rebetol group in the large naive study.  
9 We also had one drug overdose. These were illicit  
10 drugs that occurred in the Intron A/Rebetol group.

11 I would now like to summarize the dose  
12 reductions and discontinuations that occurred due to  
13 adverse events.

14 In the relapse study we looked at dose  
15 reductions that were greater than or equal to three  
16 days, the reason for this being that this was a 168-  
17 day treatment, and in reviewing the data I could see  
18 very clearly that we often would have somebody that  
19 had a gastric upset due to influenza or something, and  
20 therefore, we thought that it was clinically relevant  
21 to look at those dose reductions that lasted for at  
22 least three days.

23 As shown in this slide, the Intron/Rebetol  
24 group versus the Intron A/placebo. If you look at the  
25 relapse study we had a total of 26 dose reductions in

1 the study. Twenty of those were in the Intron  
2 A/Rebetol group, 12 percent, and six were in the  
3 Intron A/placebo.

4 The excess of dose reductions that we see  
5 in the Intron A/Rebetol group are primarily due to our  
6 criteria that was required for dose reducing for  
7 decreases in hemoglobin.

8 We also looked at our naive patient  
9 population and, because they were blinded, we had to  
10 look at any dose reduction. So this includes all dose  
11 reductions, including those less than three days.

12 In the Intron/Rebetol patients there were  
13 16 percent that required dose reduction, and in the  
14 Intron A/placebo group there were eight percent.

15 I would postulate that, based on the fact  
16 that these patients had previously not received  
17 interferon, we have as an explanation that we have a  
18 little higher dose reduction rate, and we were not  
19 particularly surprised about this.

20 Discontinuations in both studies are shown  
21 here. In the relapse study we had 16 patients who ere  
22 discontinued, 11 in the Intron A/Rebetol group, and  
23 five in the Intron A/placebo, six percent and three  
24 percent, respectively.

25 Again, we saw a little higher

1 discontinuation rate during the first 24 weeks of  
2 therapy in the naive patient population, nine and six  
3 respectively.

4 The next slide shows you the reasons for  
5 the discontinuations in the relapse study. I would  
6 remind you that there the populations are pooled for  
7 the two studies in this slide. There were nine  
8 percent discontinuations in the United States and four  
9 percent discontinuation in the international study in  
10 the Intron A/Rebetol protocol.

11 We had five that were due to psychiatric  
12 problems, one that was due to cough. There has been  
13 an association with ribavirin in increased cough, and  
14 we did see some cough in our study. This is the  
15 patient who had the tachycardia secondary to  
16 hyperthyroidism.

17 One patient was discontinued for  
18 arthralgia, two for neutropenia, and we had one  
19 patient where the investigator called the patient a  
20 discontinuation when he stopped the drug on day 167 of  
21 the study. The patient would have completed the study  
22 on day 168.

23 Had this patient been in a longer duration  
24 study, this patient would have been a dose reduction,  
25 but the investigator elected to call them a

1 discontinuation.

2 In the Intron/placebo group we had four  
3 percent that discontinued in the United States and two  
4 percent that discontinued in international. We had  
5 one suicidal ideation, one insomnia, one dehydration,  
6 one nausea, and one musculoskeletal.

7 In summary -- Excuse me. I'd like to now  
8 move to the expanded access program. As I indicated,  
9 we have 25,000 patients for whom we provided Rebetol  
10 for use in combination with Intron A. We looked at  
11 the serious adverse events in these protocols, and  
12 feel that they really reflect the pattern observed in  
13 the controlled trials.

14 I think the important message from the  
15 expanded access is that we did not see any new or  
16 unusual side effects. They're the side effects that  
17 we saw in the controlled trials, although in a much  
18 larger population, and it appears on the basis of this  
19 that the treatment protocols that we put in place and  
20 the requirements we had for inclusion and exclusion of  
21 patients and for monitoring of patients have been  
22 working in expanded access.

23 Obviously, anemia is seen with these two  
24 drugs in combination, due to the ribavirin. Flu-like  
25 symptoms have been reported, cardiovascular events,

1 much as I indicated previously, chest pain, syncope,  
2 dyspnea.

3           Dyspnea was also reported in our trials,  
4 probably due to the decreases in hemoglobin, but when  
5 we tried to equate the severity of dyspnea with the  
6 drop in hemoglobin, we were unable to do so.

7           GI symptoms have been reported, abdominal  
8 pain, nausea, vomiting. As we mentioned earlier,  
9 psychiatric side effects, depression, suicidal  
10 ideation and suicide have been reported in the  
11 expanded access program.

12           I would now like to talk about the deaths  
13 which have occurred in our programs. This study  
14 combines the relapse studies, the naive studies, and  
15 the expanded access program.

16           On the lefthand side of the slide, the  
17 study is listed, relapse, naive, and expanded access.  
18 We then grouped the deaths according to when they  
19 occurred: Pretreatment -- We did have some Rebetol  
20 monotherapy deaths. When we licensed the compound, we  
21 also took over the compassionate use program that the  
22 other company had started for monotherapy, Intron  
23 A/Rebetol and Intron A/placebo.

24           These are deaths that occurred during  
25 treatment on this slide of the slash, and during

1 follow-up on the other side. There were a total of 23  
2 deaths. One occurred pretreatment. Two were in  
3 Intron A monotherapy -- or excuse me, Rebetol  
4 monotherapy, leaving us with 18 deaths.

5 Two deaths occurred in the Intron  
6 A/placebo group during the controlled studies,  
7 actually in the naive study, leaving us with 18 deaths  
8 that occurred in the Intron A/Rebetol group.

9 Twelve deaths occurred during treatment,  
10 and six deaths occurred during the follow-up. We had  
11 one death in the relapse studies during the follow-up.  
12 This was an illicit drug overdose. It's difficult to  
13 assess whether it was a suicide or whether it was  
14 simply a drug overdose.

15 We had one death that occurred in the  
16 naive study during the treatment and two that occurred  
17 during the follow-up. We had 11 during treatment in  
18 the expanded access and three during follow-up.

19 The next slide summarizes the reasons for  
20 the deaths, these 18 deaths that occurred in the  
21 Intron A/Rebetol group. They are divided as deaths  
22 that occurred during treatment as opposed to those  
23 which occurred during follow-up.

24 We had two cardiovascular deaths, two  
25 psychiatric deaths -- these were suicides -- one

1 pulmonary death. We had a transplantation that was  
2 reported in the literature as having received  
3 interferon alfa and ribavirin.

4 We had two hemorrhages, two CNS and one  
5 GI. The GI one was probably secondary to bleeding  
6 varices. We had two infections and one auto accident.

7 In follow-up we had one cardiac death,  
8 three psychiatric deaths -- these were drug overdoses,  
9 could have been interpreted as suicides -- one CNF  
10 hemorrhage and one death that we have not been able to  
11 obtain additional information on.

12 I would remind you, in the expanded access  
13 program we are relying on the physician who has the  
14 drug to report these to the sponsor.

15 In summary with regard to the safety, we  
16 feel, based on the data that we have in our database  
17 and the data that I have shown you, that the side  
18 effects of this combination therapy are consistent  
19 with the profile of each drug as monotherapy.

20 We do not see any apparent synergistic  
21 toxicity when we combine Intron A and Rebetol. We  
22 recognize that the defining toxicity of the  
23 combination is the hemolysis that is associated with  
24 the Rebetol.

25 We have found in our clinical trials and

1 in our expanded access that we can manage this  
2 hemolysis with careful patient monitoring and dose  
3 modification.

4 In conclusion, it is our opinion that  
5 Intron A/Rebetol therapy is safe and effective for the  
6 treatment of chronic hepatitis C in adult patients who  
7 have relapsed following alfa interferon therapy.

8 Thank you very much for your attention.

9 CHAIRMAN HAMMER: Thank you for a very  
10 clear presentation.

11 What I'd like to do now before the break  
12 is actually give the committee members a few moments  
13 to ask questions. I'm going to go sequentially around  
14 the table. I would ask my fellow committee members to  
15 please prioritize your questions, and maybe just ask  
16 your two or three most pressing questions at the  
17 moment. There will be more time for questions this  
18 afternoon, but I think it's important to ask the  
19 immediate questions right after the presentation.

20 So I'll begin on my left with Dr. Gretch.

21 DR. GRETCH: Jan, I have a question about  
22 the follow-up period, the five-year follow-up period.  
23 If patients enroll in that, are they ineligible for  
24 future treatment? Does that exclude them from future  
25 treatment?

1 DR. ALBRECHT: I think what will actually  
2 happen in a five-year follow-up, Dr. Gretch, is that  
3 we've invited all patients to participate, both those  
4 patients who had sustained loss of HCV RNA and those  
5 who were nonresponders or relapsers.

6 It is my belief that those patients who  
7 are nonresponders and relapsers will probably drop out  
8 of the protocol when potentially better therapies are  
9 offered. So I think at the end of the day, what we  
10 will have is follow-up on those patients who remain  
11 responding.

12 So what we will be looking for is  
13 actually long term response in the responders. We'd  
14 like to have it in the nonresponders, but we  
15 understand they may go on to other therapies.

16 CHAIRMAN HAMMER: Dr. Friedman.

17 DR. FRIEDMAN: Two quick questions. You  
18 indicated that patients with severe depression were  
19 excluded. How is severe defined?

20 DR. ALBRECHT: Well, actually, when we  
21 monitored the studies, we specified in the protocol  
22 that if patients developed depression that had a DSM  
23 IV category, they were actually excluded. However, on  
24 entry to the study we allowed the physician to make  
25 his own assessment as to whether that depression was

1 severe.

2 We also asked the physician to call us if  
3 he had a patient that he thought was questionable. I  
4 think that probably in future protocols, we will have  
5 a more defined methodology for identifying that.

6 DR. FRIEDMAN: And the other question is:  
7 Are there any data regarding a dose response for  
8 ribavirin?

9 DR. ALBRECHT: As I mentioned when I  
10 presented our clinical program, we initiated the  
11 trials using the licensed dose of Intron A plus the  
12 dose of ribavirin that had been shown to be effective  
13 in the pilot studies; because we thought there was  
14 probably a fairly urgent need to get on with this,  
15 since the efficacy looked so promising. However, we  
16 are also conducting that second study, looking to  
17 optimize the dose of ribavirin, and that study will be  
18 closing towards the end of this year.

19 So we will be able to tell whether a lower  
20 dose will be equally effective and perhaps less toxic.

21 CHAIRMAN HAMMER: Thank you.

22 DR. GRETCH: Excuse me. May I ask a  
23 second question?

24 CHAIRMAN HAMMER: Sure.

25 DR. GRETCH: As you know, Jan, with

1 monotherapy there is data that suggests that the rate  
2 at which patients clear virus, i.e., within one or  
3 three months after therapy started, is somewhat  
4 predictive of a sustained response. Have you looked  
5 at the week four and interim analysis of RNA, and is  
6 there any -- from your interim analysis that you have  
7 looked, is there any predictive value in early  
8 monitoring for predicting response here?

9 DR. ALBRECHT: Well, we have, as you know,  
10 presented some early data that suggests that, yes, you  
11 can with higher doses and so forth get earlier  
12 response rates, and we're actually going to be looking  
13 at that.

14 CHAIRMAN HAMMER: Thank you. Dr.  
15 Zimmerman, questions? Ms. Pollichino?

16 MS. POLLICHINO: The only question I have  
17 is about the -- If somebody has hemolysis and you  
18 reduce the dose, are you reducing just the ribavirin?  
19 Are you reducing the interferon also, since that can  
20 also reduce your hemoglobin?

21 DR. ALBRECHT: The procedure that we used  
22 in the protocols was that, if the only side effect  
23 that we were seeing that required dose modification  
24 was the hemoglobin, when it dropped to less than ten  
25 grams, we reduced just the ribavirin. We actually

1 found this to be quite satisfactory, although there  
2 appears to be, when you use Intron alone, a small  
3 reduction in hemoglobin, this didn't seem to cause a  
4 problem if we just reduced the ribavirin.

5 We were, of course, anxious not to reduce  
6 the Intron dose because of the need to keep that  
7 antiviral pressure on from the Intron, and this seemed  
8 to work out fine in our studies. As I mentioned, we  
9 did not have to discontinue any patient with  
10 hemoglobin as a primary reason.

11 There were a couple of those cardiac side  
12 effects that we looked at that we -- you know, they  
13 had reductions in hemoglobin, but that was not the  
14 primary reason for the discontinuation.

15 CHAIRMAN HAMMER: Dr. Bertino.

16 DR. BERTINO: Two quick questions. Well,  
17 the first one is quick. What was your compliance, and  
18 how did you measure it?

19 DR. ALBRECHT: Our compliance rates for  
20 treatment? We had the patients keep a diary, and they  
21 marked down both their Intron A and their  
22 ribavirin/placebo pill count. We then did an audit of  
23 the drug that they returned to us.

24 The ribavirin was actually in a bottle.  
25 So we did pill count, and we also required that they

1 bring back their empty Intron bottles. Now, granted,  
2 someone could have taken the Intron out of their  
3 bottles and discarded it or thrown their pills away,  
4 but we checked to be sure whether patients had  
5 received their drug.

6 Quite frankly, we didn't have that many  
7 noncompliant patients. All patients, however, were  
8 included in the analysis.

9 DR. BERTINO: I think this might go back  
10 to a previous question, but I'm actually very  
11 interested in the nonresponders or the people that  
12 relapsed in terms of pharmacodynamics of these two  
13 agents. I don't think -- This is probably not a  
14 question to answer right now, since we're kind of  
15 rushing around, but for later I'd like to ask you  
16 about the dynamics of interferon and ribavirin in  
17 terms of reduction of viral load and things like that,  
18 and optimization of dosing.

19 I realize you were dosing the interferon  
20 on the approved dosing schedule, but I wonder if that  
21 -- you know, if you could optimize therapy with these  
22 two agents, you know, better.

23 DR. ALBRECHT: Well, the quick answer to  
24 that is that, yes, we recognize there are probably  
25 ways to optimize these therapies, in particular with

1 daily dosing of the Intron; and that is actually part  
2 of our planning process that is going on, to take a  
3 look at optimization of regimen rather than the  
4 traditional 3 TIW, but for the purpose of our  
5 discussion today we're really focusing on that 3 TIW.

6 CHAIRMAN HAMMER: Thank you. Dr. Self.

7 DR. SELF: I have no questions at this  
8 time.

9 CHAIRMAN HAMMER: Dr. Hamilton.

10 DR. HAMILTON: Validation of the surrogate  
11 markers is an extremely important assumption, I think,  
12 that you have made and we must make, if we're going to  
13 utilize that as centrally as we are.

14 Could you say a few words about how the  
15 HRV RNA has, in fact, been validated as a surrogate  
16 marker, both in the natural history of HCV and in  
17 response to chemotherapy?

18 DR. ALBRECHT: I think that probably the  
19 best -- and I wouldn't call it validation. I don't  
20 think we have validation relative to the history of  
21 the disease. I think the best data that we have at  
22 the current time is the data I mentioned that is  
23 becoming apparent in the literature.

24 That is the Patrick Marcellin group from  
25 Paris that was published in The Annals last year, and

1 now data that Dr. Hoofnagel was generating.

2 What that data basically says is when we  
3 look at loss of HCV RNA six months following the end  
4 of therapy, that there is an association with long  
5 term response. What both Dr. Marcellin and Dr.  
6 Hoofnagel are showing is that in those patients that,  
7 if you look at them someplace between three to 12  
8 years later, they do remain HCV RNA negative; and if  
9 you are able to read biopsies, they actually have  
10 liver histology that looks fairly normal.

11 So it appears that loss of the marker six  
12 months post-treatment, not at the end of therapy, is  
13 important in assessing the long term outcome.

14 DR. HAMILTON: A second question is:  
15 Evidently, some of the participants in the study  
16 acquired their hepatitis C through behaviors that led  
17 to this. Could you tell us some idea about continued  
18 risk behavior in the populations that were studied?

19 DR. ALBRECHT: The protocol required that  
20 these patients should have been off any IV drug abuse  
21 -- or drug use for at least two years. Now we had to  
22 rely on the investigators and the truthfulness of  
23 those patients in order to enforce this.

24 Most of these people or a good proportion  
25 of these people, the investigators tell me, were

1 patients that had used drugs in the past and had not  
2 used them for many years, but you can see we did have  
3 some drug overdoses. The patients were not always  
4 truthful with the investigators, and the investigators  
5 weren't able to determine that.

6 I think in this population that's a risk  
7 that we have to take. We were under the impression  
8 when they became eligible for the study they were not  
9 using drugs and had not done so for at least two  
10 years.

11 CHAIRMAN HAMMER: Thank you. Dr. El-Sadr.

12 DR. EL-SADR: I have a question. I  
13 thought that there are conflicting data, though, that  
14 suggest that the PCR does not correlate with the  
15 histologic findings on biopsy.

16 DR. ALBRECHT: I'm not aware of that data.  
17 I think that we've shown fairly convincingly in this  
18 study that the loss of HCV RNA is very much connected  
19 to the loss of -- or to the improvement in histology.  
20 In fact, Dr. Goodman, our central pathologist, is  
21 here, if later in the day, you would like to see some  
22 of the biopsy slides showing both pre and post.

23 DR. EL-SADR: I guess I'm thinking of two  
24 different things. One is measuring these markers as  
25 response to therapy versus the markers as predictors

1 of the outcome of the disease itself. So you're  
2 correctly using the data that suggests that actually  
3 measurement of these markers as a response of the  
4 therapy that you provided, but I think it's another  
5 lead to maybe suggest that these markers may be truly  
6 surrogate for ultimate outcome.

7 DR. ALBRECHT: I think I would suggest  
8 that these markers are rather a surrogate for the loss  
9 of the virus and the decrease in inflammation, that we  
10 must make that leap of faith until we have the follow-  
11 up data that indeed this relates to no development of  
12 liver failure or hepatocellular carcinoma.

13 I quite agree with you. I think what  
14 we're measuring at this six month post is a very short  
15 period of time, and then we have to make the leap of  
16 faith that indeed these will predict long term  
17 outcome.

18 The only data we really have to date is  
19 the data that I quoted where patients have  
20 retrospectively been looked at, but were treated  
21 anywhere between three to 12 years ago. So we will  
22 generate that data as time goes by, but certainly, on  
23 the basis of what's in the literature, it seems to be  
24 the case that, if you lose your virus and you are  
25 negative six months following the end of therapy, you

1 are likely to be able to maintain that response for a  
2 long time.

3 DR. EL-SADR: Two other quick questions.  
4 One is: You excluded methadone use. Is that because  
5 of some pharmacokinetic -- some interaction between  
6 methadone and the drugs?

7 DR. ALBRECHT: No. Some of the exclusions  
8 that were in these protocols were because this is the  
9 first time we've really used this combination in a  
10 large population, and we were very careful about  
11 trying to get patients that would be highly compliant,  
12 not to say that the methadone patients wouldn't be;  
13 but I think there are some studies being started right  
14 now as part of our expanded access program that do  
15 allow these patients into trials.

16 DR. EL-SADR: Then the last question is:  
17 You used response -- ALT response as an entry criteria  
18 for prior -- for measurement of prior response to  
19 interferon. Right?

20 DR. ALBRECHT: Yes.

21 DR. EL-SADR: Did you look at ALT response  
22 in this study?

23 DR. ALBRECHT: I'm sorry. That's a very  
24 good question. I meant to mention that, and I didn't  
25 have it noted on the slide.

1           If you look at loss of HCV RNA 24 weeks  
2 following end of therapy, what you find is that  
3 virtually all patients are also ALT normal. In the  
4 Intron/Rebetol group all patients except three were  
5 normal, and their ALTs were 1.02, 1.04 and 1.13 times  
6 the upper limit of normal.

7           In the Intron A/placebo group where there  
8 were far fewer patients, all of these patients had  
9 normal ALT. So normalization of ALT in these studies  
10 was correlated with loss of HCV RNA.

11           CHAIRMAN HAMMER: Thank you. Before  
12 moving to Dr. Pomerantz, your suggestion to perhaps  
13 show some biopsies early this afternoon, I think,  
14 would be most appreciated by the committee, so we can  
15 take a few minutes after lunch.

16           Dr. Pomerantz?

17           DR. POMERANTZ: Yes, two somewhat  
18 different questions. First, you are obviously looking  
19 for an indication for Intron/Rebetol for people who  
20 have responded to interferon and then relapsed. Do  
21 you have data on people who had interferon, had no  
22 effect, and then were treated with both drugs?

23           DR. ALBRECHT: Those studies are currently  
24 ongoing. In fact, there's a fair number of studies  
25 that are actually being conducted as part of the

1 expanded access program.

2 DR. POMERANTZ: So that is being  
3 conducted, but you don't have data yet?

4 DR. ALBRECHT: We don't have data yet. I  
5 believe that we do have some preliminary data that is  
6 going to be -- or that's certainly in the DDW  
7 abstracts in these nonresponders, and in some of the  
8 studies it looks promising; but that's in treatment  
9 data.

10 So I'm really a little reluctant to  
11 discuss that. I think the gold standard is, if you  
12 sustain your response six months after the end of  
13 therapy, then we can start talking about response.

14 DR. POMERANTZ: The second question is:  
15 You've obviously done the studies limiting people who  
16 are HIV-1 and 2 infected and HBV infected. Since dual  
17 infection is a major problem here and around the  
18 world, what are you proposing to do when this -- if  
19 this is put on the market for this indication, for  
20 people who are HBV or HIV infected, knowing that there  
21 is some interesting data that ribavirin has  
22 antagonistic effects against certain of the nucleoside  
23 RT inhibitors and may have synergistic effects against  
24 others, which is being used both in HIV and HBV  
25 patients now?

1 DR. ALBRECHT: Maybe I should have Dr.  
2 Glue, who is our clinical -- director of clinical  
3 pharmacology, address that question.

4 DR. POMERANTZ: Because regardless of what  
5 you ask for the indication, those patients will be  
6 treated once this is there.

7 DR. GLUE: Hi. Paul Glue, clinical  
8 pharmacology at Schering-Plough.

9 Certainly, there is some in vitro data  
10 suggesting that, for instance, the activity of AZT is  
11 inhibited by addition of ribavirin.

12 DR. POMERANTZ: Right.

13 DR. GLUE: And then there's a group in the  
14 UK who have shown that D4T activity may be enhanced.

15 DR. POMERANTZ: Right.

16 DR. GLUE: Whether this actually pans out  
17 in clinical terms is still really not known at all.

18 DR. POMERANTZ: Right.

19 DR. GLUE: And I think also the nature of  
20 the in vitro experiments -- we've got two drugs --  
21 You've got a single anti-HIV drug -- is very  
22 uncharacteristic of the way HIV patients are treated  
23 these days.

24 DR. POMERANTZ: Right.

25 DR. GLUE: And so I suspect that, as long

1 as one can put in appropriate safeguards to ensure the  
2 patient is not relapsing, that some carefully  
3 controlled trials in man are probably warranted.

4 DR. POMERANTZ: That's not my question,  
5 though. What are you going to say in an indication  
6 for patients who are being treated with AZT for HIV or  
7 even 3TC for HBV? Are you going to recommend that  
8 those patients not get this treatment?

9 DR. GLUE: Until we have some clinical  
10 data, I don't think we can give any guidelines on how  
11 to manage them, because of the in vitro data  
12 suggesting that there may be an interaction.

13 DR. POMERANTZ: It's going to be a tough  
14 decision for some clinicians.

15 DR. ALBRECHT: We do have studies in HIV  
16 and HBV going on and, in fact, what we're doing in  
17 those trials is we are actually looking at virus load,  
18 both for the C and for the HIV, and the patients will  
19 react accordingly based on whether there's an increase  
20 in virus load.

21 So we're really back to the virology on  
22 this one, I think. I think the dilemma that we have -  
23 - and I agree with you -- is that many physicians will  
24 want to treat their HIV patients, and it's going to  
25 happen.

1                   So I think the best guidance we can give  
2                   is what we're giving in the protocols, and that is  
3                   watch the virus load, and act accordingly. I guess  
4                   that would be my recommendation when people do this,  
5                   and that's what the protocols say.

6                   CHAIRMAN HAMMER: Dr. Lipsky.

7                   DR. LIPSKY: Thank you. First I think I'd  
8                   like to defer some questions on some interesting  
9                   statements in the briefing document on  
10                  pharmacokinetics which need follow-up or perhaps we  
11                  can do that this afternoon or later this morning. But  
12                  today's -- to the presentation this morning, do you  
13                  have any idea on what is happening with ribavirin, the  
14                  mechanism of action, what's going on.

15                  In the preliminary studies there did not  
16                  appear to be any viral effect of this agent, and there  
17                  was some speculation that it was "immunoregulatory" or  
18                  anti-inflammatory or whatever. Do you have any idea  
19                  that might be important for pharmacodynamics?

20                  DR. ALBRECHT: I think the best answer for  
21                  that right now from us is that we have a very large  
22                  immunology group at Schering-Plough, and so we are,  
23                  obviously, looking to see if it's an immune function  
24                  issue.

25                  We also have an extensive antiviral drug

1 development group that's looking at the virology of  
2 both the combination and the drugs by themselves. I  
3 must tell you that at this moment I can't answer that  
4 question. I wish I could, because it would certainly  
5 give us a lot of information on where we need to go  
6 from here, but we don't have an answer at the present  
7 time. That doesn't mean we're going to quit looking.

8 DR. LIPSKY: And secondly, have you looked  
9 in biopsy specimens for the presence of virus?

10 DR. ALBRECHT: That work is going on just  
11 now, and I do not have the complete dataset. We have  
12 paired biopsies, as I indicated, for pathology on 277  
13 patients. We have a smaller proportion of patients we  
14 were able to get frozen tissue, but, yes, we are  
15 measuring the virus in those biopsies.

16 DR. LIPSKY: Can you tell us something  
17 about that?

18 DR. ALBRECHT: I've only looked at the  
19 data, and the FDA has not seen this data. I've only  
20 looked at the data by hand, and it appears that loss  
21 of HCV are in the serum in the patients who are  
22 negative six months plus treatment corresponds with  
23 loss in the liver biopsy when the biopsies are  
24 available. But as I said, this data has not been  
25 shown to the agency, and I have to emphasize that.

1 I've only recently been getting it. So  
2 I've really only had a partial look. I don't want to  
3 make any statements about the correlation.

4 CHAIRMAN HAMMER: Thank you. A couple of  
5 quick questions. Can you say something about the  
6 quality control of the HepC RNA assay that's been used  
7 here, because that's been an evolution over time, and  
8 what standards have been done, how good is it at its  
9 lower limits of quantification and detection? It's  
10 briefly mentioned in the packet, but this is important  
11 when we talk about undetectable.

12 DR. ALBRECHT: I'd like Dr. Reyes, who is  
13 the Vice President of our virology group, to answer  
14 that question, if I may.

15 DR. REYES: If I could have slide 170,  
16 please. Yes, I think that's a very good question.  
17 Certainly, looking at surrogate marker in terms of the  
18 hepatitis C, RNA in serum is critical for us. I'd  
19 like to point out that a number of in-process controls  
20 are performed with every analysis.

21 First of all, each sample is spiked with  
22 an RNA control, and that spiked RNA is exogenous,  
23 totally exogenous, and so gives some indications to  
24 the efficiency of the extraction and the RT PCR  
25 procedure itself. So only a number of negative

1 controls and blanks are incorporated into the  
2 procedure to look for any cross-contamination that  
3 might occur.

4 A DNA control is also included to look at  
5 PCR amplification, to see that the amplification was  
6 appropriate, and I should mention here that the  
7 qualitative assay or super qual, as NGI calls it,  
8 actually is a PCR amplification of 45 cycles followed  
9 by Southern blotting and hybridization.

10 So that's the utmost in sensitivity and,  
11 if you're negative by those procedures, you are  
12 certainly negative.

13 There is also an STHI control which looks  
14 at the size of the transfer and the hybridization and  
15 the staining itself, and that's a post PCR control;  
16 and lastly, a series of positive and dilution series  
17 controls are performed.

18 So you can see, that extensive series of  
19 controls are incorporated into every analysis.

20 CHAIRMAN HAMMER: But how reproducible is  
21 it with the spiked controls, or what's the inter-assay  
22 variation? What's the intra-patient variation over  
23 time, just some of its performance characteristics?

24 DR. REYES: The performance  
25 characteristics are exception, actually, with this

1 assay. The in-process spiked control is actually also  
2 hybridized with every analysis, and so if any control  
3 is aberrant in the analysis, you can identify with  
4 these in-process controls where those parameters need  
5 to be optimized or where something went wrong, and  
6 basically you can go back and check that.

7 We have included the specifications on the  
8 assay in terms of the linearity in terms of the cycle  
9 number, 23, 27, 35, in the quantitative assay. Rather  
10 than doing a straight 45 cycles of varying cycles,  
11 varying cycles are utilized, and that's important,  
12 because you need to be in the linear range.

13 You can see here on this slide the super  
14 quantitative assay. There is an absence of genotype  
15 related bias. The paired sample analysis was analyzed  
16 and performed in comparison to the Chrion Quantiplex  
17 assay, as well as the Roche Amplicor, and also the  
18 assays were in a linear range between 100 and 5 times  
19  $10^6$ , achieved using PCR analysis with, as I've  
20 mentioned already, the cycles of 23, 27, 35 and 45.

21 This, obviously, becomes necessary,  
22 because you don't know a priori what is the viral load  
23 in any sample that you're testing.

24 CHAIRMAN HAMMER: Thank you. Another  
25 virologic question: Have there been any mutational

1 differences noted in patients who have relapsed on  
2 Intron and Rebetol? There's very little in the  
3 literature on ribavirin resistance. I think it's  
4 related to sindbis virus, if I recall correctly. So  
5 this might be interesting.

6 DR. REYES: That is very interesting, and  
7 again that's a very important question and something  
8 that we're certainly going to be able to address now  
9 with the samples that we have in storage.

10 CHAIRMAN HAMMER: If I may take the  
11 liberty, just two other quick questions.

12 The issue of the chest pain and dyspnea,  
13 which may or may not relate to the anemia, which is  
14 brisk and it occurs, but the level of hemoglobin,  
15 particularly given the strict screening you had, makes  
16 it -- raises the question that there may be some other  
17 mechanism for some of these events.

18 Do you strictly think that it's the  
19 hemoglobin that relates to some of the adverse effects  
20 related to the cardiorespiratory system or is there  
21 potentially something odd and unique going on here?

22 DR. ALBRECHT: I don't think it's  
23 specifically all related to the hemoglobin. Whether  
24 it's odd and unique, I don't know. These are middle  
25 aged men, for one thing, and we did see these kinds of

1 events in both groups, and there have been and is in  
2 our Intron A label cardiac events associated with  
3 Intron.

4 So I think what we are looking is a  
5 mixture of -- Dr. Geraux just said these are young  
6 men. I'm sorry. It all depends, I guess, on where  
7 you're looking from.

8 CHAIRMAN HAMMER: I would concur with that  
9 statement.

10 DR. ALBRECHT: All right. These were  
11 events in these middle-aged -- relatively young,  
12 middle-aged men. To be serious, I do think that this  
13 is a mixture probably of the two drugs, the hemoglobin  
14 drops and, as I indicated, we have seen cardiac events  
15 in the control groups, and it is in the labeling.

16 So I think we have a mixture here.

17 CHAIRMAN HAMMER: And just lastly before  
18 we break, you mentioned some of the other populations  
19 you're studying or plan to study, and what about  
20 pediatrics or patients with more organ dysfunction?  
21 What other plans do you have for populations to study,  
22 and pediatrics is one of them?

23 DR. ALBRECHT: With regard to the  
24 pediatric population, I think our first approach was  
25 that we wanted to prove the drug was safe and

1 effective in adults, and we are certainly, if asked to  
2 do so, ready to look at pediatrics, and willing to do  
3 so.

4 We do have some -- There is some  
5 interesting data in the literature about the treatment  
6 of liver transplantation patients. As you probably  
7 know, all liver transplantation patients virtually,  
8 when they are transplanted, reinfect. There are some  
9 studies going on, one in the United States and several  
10 in Europe, looking at the use of the combination in  
11 these transplant patients. So those studies are  
12 ongoing.

13 CHAIRMAN HAMMER: Thank you. I think  
14 we'll take a 15-20 minute break, return here promptly  
15 at 10:25 to 10:30.

16 (Whereupon, the foregoing matter went off  
17 the record at 10:08 a.m. and went back on the record  
18 at 10:30 a.m.)

19 CHAIRMAN HAMMER: Thank you. The next  
20 agenda item is the FDA presentation, which will be  
21 done by Dr. Russell Fleischer.

22 MR. FLEISCHER: Good morning. My name is  
23 Russ Fleischer. I'm the primary clinical reviewer  
24 from the Division of Antiviral Drug Products for this  
25 application.

1           Since the applicant has presented a  
2 comprehensive overview of the NDA, our intent is not  
3 to reiterate their discussions, but instead of  
4 highlight the issues that will be presented for your  
5 consideration.

6           After I provide a brief summary of the  
7 clinical studies, Dr. Tan Nguyen, who is a pathologist  
8 in our division, will present a discussion of some  
9 issues related to the Knodell HAI score. He will be  
10 followed by the statistical reviewer, Dr. Greg Soon,  
11 who will focus on the interrelationships between  
12 various outcome measures.

13           Then I will come back and conclude our  
14 presentation by discussing the safety profile of the  
15 combination and summarizing some important clinical  
16 and regulatory issues associated with this  
17 application.

18           Now as you heard, the applicant has  
19 conducted two Phase III trials in a total population  
20 of 345 patients with chronic hepatitis C virus  
21 infection and compensated liver disease, who had  
22 responded to a previous course of interferon  
23 monotherapy and had relapsed, as evidenced by  
24 elevations in ALT levels within one year following  
25 discontinuation of therapy.

1 Patients were randomized either to receive  
2 ribavirin plus interferon or placebo plus interferon  
3 for 24 weeks of therapy followed by 24 weeks of post-  
4 therapy follow-up.

5 To review the original protocol specified  
6 endpoints of these studies, a sustained virologic  
7 response was defined as achievement of HCV RNA below  
8 the level of quantification of the experimental assay  
9 at week 24, by the end of therapy, that was sustained  
10 through the end of the follow-up period, week 48.

11 Histological improvement was defined as a  
12 greater than or equal to two-point improvement, and  
13 three of the four components of the HAI score, and an  
14 overall response was a combined histologic and  
15 virologic response.

16 I would like to turn this over to Dr.  
17 Nguyen for his discussion of the Knodell HAI score.

18 DR. NGUYEN: Thank you, Russ. My name is  
19 Tan Nguyen, and I'm not sure if it's a blessing to be  
20 introduced as pathologist around here, because with  
21 the exception of some notable pathologists in the  
22 audience here, we tend to find ourselves giving the  
23 wrong lecture to the right audience or vice versa.

24 Anyway, let me just go ahead and move on.  
25 You have seen this slide before. It was partially

1 presented by Dr. Albrecht and very elegantly -- thank  
2 you very much. But let me just briefly go through the  
3 Knodell HIA scoring system, filling in the gaps rather  
4 than repeating what she had to say.

5 For the Knodell -- all the liver biopsies  
6 in this study -- in these studies, actually, were  
7 scored using the Knodell histological activity index  
8 scoring system, and that's probably the most popular,  
9 the one that's been used universally.

10 For this scoring system you could see that  
11 there are three -- there are four components, the  
12 first three dealing primarily with the necrosis and  
13 the inflammation, and so that one, two, and three.

14 So one, two and three occasionally would  
15 be referred to in clinical literature using  
16 terminology borrowed from tumor pathology as a grading  
17 of their liver biopsy. It refers to the severity of  
18 the activity that you can see in the liver biopsy.

19 The last component, the fourth component,  
20 is fibrosis. Now this is the clinically significant  
21 and the prognostically significant component of the  
22 Knodell system. You need -- We all need to know that  
23 all four components are actually interrelated.

24 If you don't have necrosis, inflammation,  
25 you probably would not have any fibrosis. However, in

1 chronic hepatitis you will have necrosis, you will  
2 have inflammation, and you will have fibrosis. The  
3 fibrosis tends to be either the same, which is good,  
4 or it could get worse.

5 Now the scoring system is given in a very  
6 simplistic manner over here. The periportal necrosis,  
7 component one, is given a score from zero to a maximum  
8 of ten; whereas, the other components are given scores  
9 from zero to four. Now I'm not going to go into  
10 detail talking about all the way -- different ways  
11 that you can give the scores.

12 Now as far as the histological analysis is  
13 concerned, you saw Sharon's presentation earlier.  
14 They use the so called necroinflammatory score. That  
15 is, you use only the three components, one, two and  
16 three. Whereas, the other way to look at the  
17 histologic analysis is basically you use what we call  
18 total score, because the four components, as I said,  
19 represent a continuum of the disease process.

20 So you look at all total four scores added  
21 together, and that is one, two, three and four. So in  
22 the next slide what I would like to present to you is  
23 that there's two different ways to look at the liver  
24 biopsy results using two different ways for the  
25 analysis, the necroinflammatory and the total score.

1           Here I'm just going to show the study 144.  
2           This is the U.S. study. The results are basically the  
3           same for the international 145 study. So here we have  
4           the percent of patients, the ribavirin treatment arm,  
5           placebo treatment arm.

6           You can see the number. The end numbers  
7           over here are 61 and 64, because we're going to look  
8           at only the group of patients that got the paired  
9           pretreatment and post treatment biopsies. So we're  
10          not looking at those with missing data.

11          Over here you can see that this is a  
12          necroinflammatory way of analysis, and the bottom here  
13          is a total. That is the score of four components. If  
14          you look over here and you see the improvement versus  
15          no improvement, and you could barely read the footnote  
16          over there. As Sharon defined this morning in the  
17          protocol, that a change of two points, an improvement  
18          of two points in the post treatment biopsy -- that  
19          would indicate histological improvement.

20          Now let me just briefly say that this is  
21          an arbitrary cutoff point. However, it does suggest  
22          that there is an improvement histologically.

23          If you look at the proportions of the  
24          patients with improvement, no improvement in the  
25          necroinflammatory, you got 61 and 39 percent. If you

1 use a total Knodell score analysis, the proportions  
2 are not really that significantly different. You got  
3 62 and 38. You lost one patient somewhere in there.

4 Now what does that mean? That just simply  
5 tells -- the fact is, the majority of the patients in  
6 the treatment -- in the study did not have significant  
7 or did not have really progression of fibrosis during  
8 the study.

9 Another thing -- Another point to make it  
10 out is, if you look at the placebo, the proportion is  
11 also similar. So there is no differential difference  
12 in the two treatment arms regarding the progression of  
13 fibrosis, but we always want to be cautioned on the  
14 fact that the post treatment biopsies were obtained  
15 within six months after the treatment. For a disease  
16 that's got a life span probably 20 years, six months  
17 after treatment probably might not be a significantly  
18 long duration of time in order to see any progression  
19 of fibrosis.

20 Therefore, the bottom line is long term  
21 follow-up data regarding the liver biopsy, regarding  
22 the improvement histologically is really necessary  
23 before we can make any histological improvement  
24 assessment.

25 I will turn the podium over to Dr. Greg

1       Soon, who is going to present the clinical -- I mean  
2       the statistical points.

3                 DR. SOON: Good morning. I'm Greg Soon,  
4       statistical reviewer for this NDA.

5                 This is a brief overview of my talk.  
6       First I will summarize the efficacy results, HCV RNA  
7       and the biopsy. Further, I will discuss the  
8       association of these two measures.

9                 Secondly, I will show that early HCV RNA  
10       responses are more likely to be maintained than those  
11       occurred only at the later stages of trial.

12                In the third part of my talk, I will  
13       discuss the relationship between baseline and week 48  
14       HCV RNA and the role of genotype.

15                At the end, I will concentrate on the  
16       relationship of the HCV RNA and ALT and their  
17       consistency over time.

18                Recall that the efficacy measures for  
19       these trials include HCV RNA as measured by an  
20       experimental assay, biopsy and ALT. HCV RNA and ALT  
21       were measured relatively frequently during the trial.  
22       Biopsy was made at baseline and at week 48.

23                The primary efficacy endpoint for this NDA  
24       is overall response, which is defined to be sustained  
25       HCV RNA response with biopsy improvement.

1 Here is a standard HCV RNA response. It means that  
2 all values from week 24 through 48 were below the  
3 limit of quantification.

4 Biopsy improvement is defined to be  
5 improvement by two points or more throughout the  
6 history of the patient. I will focus primarily on the  
7 U.S. data. The results of the international study are  
8 similar. I will also simply refer to the two  
9 treatments as the ribavirin and placebo, without  
10 mentioning interferon which were used in all patients  
11 in these trials.

12 Now I will briefly review the efficacy  
13 results for HVC RNA and biopsy. The sustained HCV RNA  
14 response rate is 42 percent for the 77 subjects in the  
15 ribavirin arm, while this is only four percent in the  
16 placebo arm.

17 Contrary to this relatively large  
18 difference for the sustained HCV RNA response rates,  
19 the rates of biopsy improvement are more similar  
20 between the treatment arms, 49 percent versus 36  
21 percent.

22 It should be noted that 21 percent and 50  
23 percent of biopsy values are missing, while only 12  
24 percent and 9 percent are missing for HCV RNA. This  
25 table does not show how these two measures are related

1 to each other. In the next two slides I will show you  
2 more details, the pattern of their relationship.

3 The first slide is for the ribavirin  
4 treated patients. This is a cross-tabulation of  
5 sustained HCV RNA response by biopsy improvement.  
6 From this table we can see that 30 percent of the  
7 patients responded in both outcome measures. This is  
8 the overall response rate, which is the primary  
9 efficacy endpoint.

10 We can also see that 23 percent, given a  
11 response on either of the two measures, so the two  
12 measures agree on 53 percent of the subjects.

13 On the other hand, the two measures were  
14 discordant on 18 plus 6. That is 24 percent of the  
15 subjects. The majority of the discordant results  
16 occurred in patients who responded in biopsy but not  
17 in HCV RNA.

18 Now let's turn the placebo treated  
19 patients. Here are the overall response rates, only  
20 three percent; but there are 47 percent of the  
21 subjects who did not respond to either of the two  
22 measures. Again, the agreement rate is about 50  
23 percent.

24 A new and larger discordance can be seen  
25 here than for the ribavirin treated patients, which is

1 33 plus one. Call it 34 percent, and 33 percent of  
2 all patients improved in biopsy, but they are not  
3 sustained HCV RNA responders.

4 In summary, these tables show that, first,  
5 -- HCV RNA and biopsy agree on about 50 percent of the  
6 subjects. Second, the measures disagree on 24 percent  
7 and 34 percent of the subjects. Most of the  
8 discordance was made up of biopsy responders but are  
9 not sustained HCV RNA responders. This pattern is  
10 especially striking in the placebo treated patients.

11 Now I'll move on to the second part of my  
12 talk, which is how early HCV RNA declined. Relates to  
13 week 48 results. This graph is for the U.S. study.  
14 The left portion of the graph represents ribavirin  
15 treated patients, and the right portion represents  
16 placebo group.

17 The height of the bars shows how many  
18 patients achieved HCV RNA below LOQ for the first time  
19 at weeks 4, 12 and 24. Inside each bar the red  
20 portion represents how many patients achieved HCV RNA  
21 below LOQ at week 48.

22 First we note that most people who  
23 achieved HCV RNA below LOQ did so by week 12. Still,  
24 quite a few patients achieved HCV RNA below LOQ for  
25 the first time only at week 24.

1           Next we ask if the time to HCV RNA below  
2 LOQ predicts the week 48 HCV RNA below LOQ. Let's  
3 begin with the ribavirin arm first.

4           At week 4 there are 24 subjects achieved  
5 HCV RNA below LOQ, and of these 79 percent also had  
6 HCV RNA below LOQ at week 48. At week 12 there are 31  
7 subjects achieved HCV RNA below LOQ for the first  
8 time, and the rate of HCV RNA below LOQ at week 48  
9 decreased to 48 percent.

10           For subjects who achieved HCV RNA below  
11 LOQ for the first time at week 24, this read zero  
12 percent.

13           Now let's look at placebo treated  
14 patients. The rates are 60 percent and zero percent  
15 at week 4 and 12. The rate is zero percent for  
16 subjects who did not achieve HCV RNA below LOQ by week  
17 12.

18           A second study, the international study,  
19 shows a similar relationship, and it confirms the  
20 previous findings. The week 48 LOQ rates for the  
21 ribavirin arm are 93 percent, 49 percent and zero  
22 percent. The rates for placebo are also in decreasing  
23 order, at 31 percent, four percent and zero percent.

24           In summary, from this slide and the  
25 previous slide it appears that subjects who achieve

1 HCV RNA below LOQ earlier have a better chance of  
2 having the week 48 HCV RNA below LOQ. Those patients  
3 who did not achieve HCV RNA below LOQ by week 12 are  
4 unlikely to achieve HCV RNA below LOQ at week 48,  
5 regardless of the treatment assignment.

6 The third topic of my talk is on the  
7 relationship between baseline and week 48 HCV RNA and  
8 the role of genotype. This is a plot for HCV RNA  
9 Baseline value versus week 48 value.

10 The yellow -- The horizontal line which is  
11 hard to see is limit of quantification. We can see  
12 here that there is a weak positive correlation between  
13 the baseline and the week 48 HCV RNA. There is no  
14 single baseline value which determines whether  
15 subjects will be below or above the LOQ at week 48.

16 Now consider the color, which again is  
17 hard to see here, of the points. The red dots or the  
18 circles represents the non-genotype 1 patients, and  
19 the white or the triangles represents genotype 1.

20 Non-genotype 1 tend to be below LOQ line,  
21 while the genotype 1 is more frequently above LOQ  
22 line. Therefore, non-genotype 1 is associated with a  
23 greater proportion of subjects below LOQ line at week  
24 48 than the genotype 1 subjects. This relationship  
25 was previously discussed by the applicant.

1 My fourth and last topic compares ALT and  
2 HCV RNA. ALT is displayed on the x axis, and HCV RNA  
3 at week 48 is displayed on the y axis. The yellow  
4 vertical line is upper limit of normal for the ALT,  
5 and again the horizontal represents the limit of  
6 quantification for the HCV RNA.

7 For the ALT values left to this line are  
8 normal ALTs, and values to the right are elevated  
9 ALTs. We see here that ALT and HCV RNA response at  
10 week 48 are in very good agreement. Both are high or  
11 both are low.

12 I'm not presenting placebo, because almost  
13 all of them are high on both measures. Because I see  
14 that ALT is evenly spread across a range of the  
15 values, but the four values of HCV RNA, they are  
16 either below LOQ or have relatively high values.

17 On the next slide I will show that ALT may  
18 not be as predictive as HCV RNA. When the U.S. study  
19 and the international study are combined, there were  
20 89 subjects who had HCV RNA below LOQ at weeks 24 and  
21 48. Of these subjects, only three had HCV RNA above  
22 LOQ at week 36.

23 In contrast, there are 95 subjects who had  
24 a normal ALT at weeks 24 and 48, but 14 of them had  
25 ALT greater than upper limit of normal at week 36.

1                   Now I will return the podium to Russ  
2                   Fleischer.

3                   MR. FLEISCHER: Thank you, Dr. Soon, Dr.  
4                   Nguyen.

5                   Before I move to our talk or discussion of  
6                   safety, I'd like to take a moment to try to summarize  
7                   a few of the points you just heard.

8                   First, patients treated with a combination  
9                   had significantly higher virologic and histologic  
10                  responses as compared to placebo recipients. Of note,  
11                  more patients in both treatment groups exhibited  
12                  histological improvement than either sustained  
13                  virologic response or an overall response.

14                  Moreover, fibrosis, even though it's an  
15                  important aspect of this disease, the inclusion of the  
16                  criteria of component four in the analysis of the HAI  
17                  score did not appreciably affect the results.

18                  Next, patients who received an early  
19                  virologic response by week 12 were more likely to  
20                  maintain that response throughout the remainder of the  
21                  study.

22                  Third, patients with non-genotype 1 virus  
23                  generally responded better to treatment than patients  
24                  with genotype 1, and this is generally consistent with  
25                  what you've already heard today.

1                   Finally, although patients who had normal  
2 ALT values at week 48 generally also had HCV RNA  
3 values below the LOQ at week 48, ALT levels were more  
4 variable throughout the study period.

5                   So let's move on to safety. The safety  
6 database for this application included approximately  
7 30,000 patients, and as you heard from the applicant  
8 this morning, there were about 356 patients in the two  
9 relapse studies. Approximately 1800 are in the two  
10 ongoing naive studies, and the remainder received  
11 ribavirin alone or with interferon in a variety of  
12 treatment protocols, worldwide investigator initiated  
13 studies, and open label use.

14                   The safety profile for the combination was  
15 primarily derived from the two relapse studies. We  
16 received serious adverse event and death data from  
17 these other sources, but the types of events reported  
18 were consistent between all the sources.

19                   Adverse events were very common, occurring  
20 in virtually all the patients in the two relapse  
21 trials, and this slide presents a list of some of the  
22 more commonly occurring events reported in these two  
23 studies.

24                   The data in this slide are from the U.S.  
25 study. The types of events were similar in the

1 international trial, although the reported frequencies  
2 were lower in both treatment arms.

3 It's notable that the majority of these  
4 events occurred more frequently in the combination  
5 arm, and as noted previously by the applicant, there  
6 were more dose reductions and discontinuations due to  
7 adverse events in the combination arm.

8 Just to point out a couple, headache,  
9 about 66 percent versus 47; myalgia occurred in about  
10 twice as many patients as did fatigue, and rigors and,  
11 as the applicant mentioned, about 25-27 percent of  
12 patients had alopecia.

13 In addition to these events, anemia, which  
14 is very common and known complication of ribavirin  
15 therapy, was common in these studies. As I'll discuss  
16 in a moment, it was markedly more frequent in the  
17 combination arm.

18 So in interpreting the significance of  
19 this event, it's very important to remember that the  
20 applicant enrolled patients with normal baseline  
21 hemoglobin levels and excluded patients with  
22 significant cardiovascular disease.

23 As you can see in the U.S. study,  
24 ribavirin treated patients have significantly greater  
25 hemoglobin reductions from baseline compared to

1 placebo treated patients. 64 percent versus 8 percent  
2 had a two to four gram per deciliter reduction from  
3 baseline, and 12 percent of the ribavirin group versus  
4 one percent of the placebo group had a greater than  
5 four gram per deciliter reduction from baseline.

6 Hemoglobin, 10 grams per deciliter or  
7 less, was the level at which dose modifications were  
8 to occur. Approximately ten percent of the ribavirin  
9 treated patients had a reduction in their hemoglobin  
10 at some point during the 24 weeks of therapy to less  
11 than ten grams per deciliter, compared to no patients  
12 in the placebo groups. The rates in the international  
13 trial were similar.

14 Although hemoglobins generally stabilized  
15 by week four and in most patients returned to normal  
16 within four to eight weeks after ribavirin therapy was  
17 stopped, levels tended to drop quickly, within the  
18 first one to two weeks of therapy.

19 I'd like to turn to a discussion of  
20 psychiatric related events, which also occurred  
21 frequently in the two relapse studies. These appear  
22 to increase with frequency over time.

23 The interferons are known to cause a  
24 spectrum of CNS dysfunctions, ranging from mild  
25 irritability and memory impairments to more severe

1 complications such as depression, psychosis and  
2 delirium.

3 Psychiatric related events occurred in  
4 over 60 percent of the patients in the U.S. trial.  
5 Again, it's important to note that patients with  
6 preexisting severe depression or other severe  
7 psychiatric disorders were excluded from enrollment.

8 These events also occurred frequently in  
9 the international study, but the rates were generally  
10 lower, which is a phenomenon that's been observed in  
11 other international trials.

12 Also, although these events occurred with  
13 more frequency in the combination arm, the rates were  
14 generally consistent with those that have been  
15 previously reported for interferon monotherapy.

16 Suicidal behavior, including ideation,  
17 attempted suicides and completed suicides, occurred in  
18 a small number of patients in the entire 30,000  
19 patient safety database.

20 Let me now turn to deaths. As you heard,  
21 there were 23 deaths that have been reported in the  
22 safety database, and you can see the distribution by  
23 source in this slide. Given the frequency of  
24 psychiatric events and anemia, we were concerned that  
25 these complications might be contributing to patient

1 deaths.

2 There were two on-therapy completed  
3 suicides that occurred during investigator initiated  
4 studies. One of these patients also had treatment  
5 emergent depression. One patient who died in the  
6 relapse studies died from illicit drug overdose during  
7 the follow-up period. This patient also had treatment  
8 emergent depression.

9 There were two additional deaths due to  
10 illicit overdoses that occurred in the ongoing naive  
11 patient trials. Both patients had a history of  
12 depression prior to entry in the study. One patient  
13 died on therapy, and the other died during the follow-  
14 up period. For these two patients the treatment  
15 groups remain blinded.

16 There were two on-therapy deaths due to  
17 myocardial infarctions, and both occurred during the  
18 naive trial. One was in a patient on combination  
19 therapy who had a history of diabetes, hypertension,  
20 and had had a previous myocardial infarction.

21 Four weeks prior to death, the patient had  
22 a six gram per deciliter drop in his hemoglobin, and  
23 his hemoglobin remained low, ranging between nine and  
24 a half and 10.3 grams per deciliter, until he died.

25 The other MI was in a placebo recipient

1 who also had a history of diabetes and hypertension,  
2 but in contrast, this patient's hemoglobin only  
3 dropped three points, from 16.5 to 13.2 grams per  
4 deciliter at the time of death.

5 The other causes of death were due to a  
6 variety of reasons, including trauma, infections,  
7 ruptured aneurisms, meningitis, etcetera.

8 So to conclude my remarks, I'd like to  
9 turn to a few of the regulatory and clinical issues  
10 that were associated with this application. So today  
11 we're going to ask you to provide us some guidance on  
12 what we know and what we don't know about this  
13 combination.

14 First, to focus on dose, the applicant has  
15 studied this combination using a licensed dose and  
16 schedule of interferon. The dose of ribavirin was  
17 based on the maximally tolerated dose that was used in  
18 previous monotherapy studies, and dose ranging studies  
19 have not been completed. So there are no data on the  
20 safety or efficacy of other dose levels of these  
21 agents when used in combination.

22 Finally, patients with creatinine  
23 clearance of less than 15 -- correct, 50 milliliters  
24 per minute were excluded from the trials, and there  
25 are no data from formal renal impairment studies.

1           The next issue is duration. The applicant  
2           has submitted data from six months of therapy with six  
3           months of post-therapy follow-up. There are no data  
4           on the safety or efficacy of either shorter or longer  
5           treatment durations.

6           In the two relapse studies, time to  
7           initial virologic response was predictive of sustained  
8           virologic response and, as previously shown, all of  
9           the patients who were sustained virologic responders  
10          had achieved their initial virologic response by week  
11          12 of therapy.

12          Finally, population: The applicant  
13          enrolled only patients who are tolerant of interferon  
14          and had responded to previous interferon therapy. All  
15          of the patients had compensated liver function. Also,  
16          patients had stable cardiac function, and patients  
17          with significant psychiatric disorders, including  
18          severe depression, were excluded.

19          Adverse events were very common in the two  
20          trials and were generally consistent with the known  
21          adverse event profiles of the two agents, but were  
22          generally higher in the combination treated patients.  
23          Anemia and psychiatric events, including depression  
24          and suicidal behavior, were important events  
25          associated with the use of the combination.

1 In conclusion, the two studies submitted  
2 to this NDA demonstrated that treatment with  
3 interferon plus ribavirin produced higher sustained  
4 virologic response rates, higher rates of histologic  
5 improvement, and overall response rates compared to  
6 patients treated with interferon plus placebo.

7 We have good data on a selected population  
8 of HCV infected patients. However, the safety and  
9 efficacy of this combination in patients with more  
10 advanced hepatic disease, patients who have failed  
11 previous interferon monotherapy, and patients with  
12 significant underlying cardiovascular dysfunction or  
13 decreased cardiac reserve or patients with significant  
14 psychiatric disorders remains to be determined.

15 Finally, we do not fully understand what  
16 the optimal dose or duration of treatment is and what  
17 parameters are best for monitoring patients during  
18 treatment and follow-up.

19 Finally, the long term impact of treatment  
20 with this combination and the ultimate clinical  
21 endpoints of interest, progression to cirrhosis,  
22 hepatocellular carcinoma, or death, is unknown; and  
23 it's these issues that we turn to you for guidance.

24 In the last slide, I'd just like to  
25 acknowledge the members of the review team who did not

1 present here today. I would also like to thank my  
2 colleagues in the Center for Biologics who provided  
3 valuable assistance during the review of this NDA, and  
4 I'd like to thank Terrie Crescenzi, the project  
5 manager, for this application. Thank you.

6 CHAIRMAN HAMMER: Thank you very much.  
7 I'd like to open it up to questions from committee  
8 members for the FDA presenters, and I'll just leave  
9 this open rather than go formally around the table.  
10 So raise your hand, please, if you've got questions  
11 for the reviewers. Dr. El-Sadr.

12 DR. EL-SADR: I don't remember from the  
13 applicant's presentation the issue of adverse --  
14 rigors as adverse events. Do we know more about it?  
15 Rigors -- 43 percent of the ribavirin had rigors  
16 versus 13 percent. Was that in association with  
17 infection or --

18 DR. BEHRMAN: Interferon.

19 DR. EL-SADR: But it was seen more in --

20 DR. BEHRMAN: Right.

21 DR. EL-SADR: It was still seen more in  
22 the ribavirin group.

23 DR. BEHRMAN: Exactly, as were most of  
24 those events. In other words, where patients --

25 DR. EL-SADR: You're attributing to the

1 background interferon therapy?

2 DR. BEHRMAN: Well, I think the point we  
3 were trying to make is that these are events seen in  
4 interferon. They appeared to be more prevalent with  
5 ribavirin. So there is, if you will, some synergy,  
6 but no, we did not believe it was related to  
7 intercurrent infections, if that's what you're asking,  
8 or other processes. No.

9 DR. EL-SADR: I mean, does this suggest  
10 that an effect on sort of promoting the side effects  
11 of interferon?

12 DR. BEHRMAN: Most of the interferon --  
13 typical interferon side effects were, in fact, worse,  
14 yes, in the combination arm, some substantially, some  
15 a little bit. So, yes, we believe it potentiates  
16 those effects. I don't know if the applicant would  
17 like to comment as well.

18 CHAIRMAN HAMMER: Dr. Hamilton.

19 DR. HAMILTON: I have some concerns about  
20 the deaths that occurred in both the naive and relapse  
21 and expanded access. Were any efforts made to obtain  
22 autopsies on any of those individuals and, if so, what  
23 were the results?

24 DR. CORT: We obtained autopsies on all  
25 patients that actually did have an autopsy. The one

1 patient who died of myocardial infarction who was on  
2 Intron and placebo had an autopsy. The other one did  
3 not. The findings were consistent with an autopsy.

4 The one undetermined death was a 73-year-  
5 old female patient with a cirrhosis and a preexisting  
6 thyroid disease who was found dead in a bathtub  
7 approximately five months after discontinuing therapy.  
8 The autopsy failed to reveal any immediate cause of  
9 death other than the diseases that were there  
10 previously.

11 DR. HAMILTON: So it makes for a total of  
12 how many autopsies among those?

13 DR. CORT: We had a total of three autopsy  
14 results in patients who actually were autopsied.  
15 Majority of the patients were not. There were also  
16 some autopsies, particularly in the drug overdoses,  
17 that we're still awaiting results to confirm that.

18 CHAIRMAN HAMMER: Would you please  
19 identify yourself for the transcript?

20 DR. CORT: Sorry. Susannah Cort. I'm the  
21 project physician for these two studies.

22 CHAIRMAN HAMMER: Thank you. Dr. Bertino.

23 DR. BERTINO: Back to the side effect  
24 question. Is there any data on the pharmacokinetics  
25 of interferon with and without ribavirin? I mean, is

1 that a possible explanation?

2 DR. BEHRMAN: I think we should ask our  
3 biopharm group or the applicant's biopharm group to  
4 respond.

5 DR. GLUE: Hi. Paul Glue here from  
6 Schering-Plough.

7 Yes, we do have some information on the  
8 pharmacokinetics of both interferon and ribavirin,  
9 alone and in combination. We carried out a formal  
10 parallel group drug interaction study.

11 If I could have slide 225, please. We had  
12 a total of 36 patients, 12 of whom received ribavirin  
13 alone, a single dose, followed by four weeks of  
14 multiple dose therapy, another 12 subjects who  
15 received interferon alone, and 12 subjects who  
16 received combination.

17 These are the standard doses, 1200mg/day,  
18 3 million units three times a week with a combination  
19 of the same doses. This is a study carried out in  
20 patients with hepatitis C.

21 These are the Rebetol concentrations after  
22 the single dose in patients who received Rebetol alone  
23 or the combination, and essentially the curves  
24 overlap. Following multiple doses, again the shapes  
25 of the curves are identical, and they essentially

1 overlap.

2           These are the mean interferon  
3 concentration time profiles in patients who received  
4 Intron alone, the white triangles, single dose,  
5 multiple dose -- I'm sorry, single dose in  
6 combination, the purple triangles, similar curve  
7 profiles and essentially overlapping results.

8           After multiple doses those who received  
9 Intron alone, the open triangles, and the people who  
10 received combination essentially similar results.

11           If you could give me slide 222, please.  
12 These are the derived pharmacokinetic parameters for  
13 patients for Intron A in those people who got  
14 combination treatment and those who received Intron  
15 alone. The week one AUCs and Cmax -- so this is the  
16 single dose data -- are essentially similar, and under  
17 multiple dose conditions, again very similar derived  
18 PK parameters, and the same for Rebetol.

19           The people who received Rebetol alone  
20 during the course of the study and those who received  
21 the combination -- the mean AUCs and Cmax for other  
22 monotherapy or combination therapy was similar, both  
23 after single dose and multiple dose.

24           DR. BERTINO: Can you go back to one slide  
25 back so I can just look at that.

1 DR. GLUE: The other thing to remember  
2 from the study is that both Intron and ribavirin are  
3 highly variable drugs. We don't have the estimates of  
4 variability up there, but under both single and  
5 multiple -- under single dose conditions, the  
6 variability is in the 50-60 percent range. Under  
7 multiple dose conditions, it's 30-40 percent range.

8 DR. BERTINO: Thank you.

9 CHAIRMAN HAMMER: Dr. Self.

10 DR. SELF: I'd like to return to the issue  
11 of study endpoint. There are no data here on the  
12 effect on clinical endpoints, although the effect on  
13 viral load and histology is striking. The question  
14 was asked earlier what the relationship might be, and  
15 I think the response from the sponsor was something  
16 about requiring a leap of faith.

17 To the FDA reviewers: How do you feel  
18 about the impact on viral load, what it may mean for  
19 clinical outcomes in these patients?

20 DR. BEHRMAN: We're given this, obviously,  
21 a lot of thought. An important point to make is that  
22 we are not asking the committee whether there is "a  
23 validated surrogate" in this disease state. We don't  
24 believe we've given you enough information to answer  
25 that.

1 We are also not asking whether or not you  
2 believe that this should be an accelerated approval  
3 based on an unvalidated surrogate. We're asking you  
4 whether you believe there's enough evidence of safety  
5 and efficacy to support traditional approval.

6 Having said that, the sponsors who are  
7 developing drugs for HBV and VCV are in a very  
8 difficult position, because, obviously, we can't ask  
9 them to wait 20 years for their endpoints and then  
10 come in. So there are some limitations.

11 In this case, we believe that the sponsor  
12 -- or the applicant is presenting you not only with  
13 viral data but also biopsy data which show a  
14 reasonable degree of correlation, and we believe in  
15 this package there is sufficient information about --  
16 albeit short term -- clinical benefit to make an  
17 assessment -- a risk benefit assessment to support  
18 traditional approval. But that does a little bit beg  
19 your question, which is what does this mean for the  
20 long term.

21 That's something, actually, we hope the  
22 committee would address, because if indeed this drug  
23 were to go on to be approved, some of these  
24 limitations and qualifications should be incorporated  
25 into the package insert.

1 DR. JOLSON: I just have one other comment  
2 to Dr. Behrman, and that's something in the questions  
3 this afternoon that the committee can discuss. One of  
4 the question is what sorts of additional studies need  
5 to be done post marketing.

6 Because we sense that there have been  
7 several questions about -- that relate to the  
8 important issue, what's the overall clinical utility  
9 of this regimen or other similar sorts of regimens,  
10 that perhaps the committee could make suggestions of  
11 studies that would be feasible to do post marketing  
12 that would help better resolve this issue.

13 DR. BEHRMAN: If I could just add that,  
14 because we're not really -- We're presenting this  
15 application, but in a sense Schering-Plough is doing  
16 us a bit of a favor, because we are also looking for  
17 guidance in terms of what future sponsors should be  
18 looking to do and what we should be asking of them.

19 Someone always has to come first, and  
20 they're going to have the most limited database.

21 Could I just return to Wafaa's question  
22 for a moment. I finally understood that. I  
23 apologize.

24 When we looked at the AEs, we looked at  
25 both the relapse patients, which we focused on, but

1 also the naive patients to sort of see how much  
2 correlation and how much reinforcement.

3 In general, the AEs that were most  
4 prominent in the combo arm were ones where both  
5 ribavirin and interferon were known to have effects,  
6 such as rash, although it's a lower frequency. It  
7 didn't show up as much, but there was a dramatic  
8 difference.

9 Depression, we paid particular attention  
10 to. Rigors didn't stand out to us. Although there is  
11 a difference, it wasn't a big difference. So it  
12 tended more to be those AEs you would see in the  
13 individual -- with the individual agent.

14 DR. EL-SADR: One other question. Amongst  
15 the, I guess, probably 15,000 people who got the  
16 combination, at some point did any women become  
17 pregnant during these trials?

18 MR. FLEISCHER: The answer is yes. Does  
19 Schering want to address that?

20 DR. ALBRECHT: May I have slide 94,  
21 please. This is a summary of the pregnancies that  
22 occurred in both the controlled trials and the  
23 expanded access. It's rather a busy slide. So I'll  
24 take a moment to explain it.

25 On the left is the outcome, and in the

1 first set of data are the patients themselves. As you  
2 will recall, we very strenuously enforced  
3 contraception. Patients were required to be able to  
4 use adequate contraception, and female patients while  
5 on study had pregnancy tests done once a month.

6 These are the results of the Intron  
7 A/Rebetol group, the Intron A/placebo group. As you  
8 will remember, in the naive patients that study  
9 remains blinded in some cases. So we do not know  
10 about this patient.

11 If you look at healthy births, basically  
12 no patient became pregnant on the Intron/Rebetol or  
13 the Intron/placebo for which we have a report yet of  
14 a healthy birth.

15 Patients who became pregnant and had  
16 miscarriages were three in the Intron/Rebetol, two in  
17 the Intron/placebo and one is blinded. We did have  
18 some patients become pregnant on the Intron/Rebetol.  
19 Five of these patients had voluntary terminations.

20 We have one pregnancy ongoing in the  
21 Intron/Rebetol group. This patient actually became  
22 pregnant three months post therapy. So the pregnancy  
23 is ongoing at the present time.

24 We also kept a registry of spouses or  
25 partners who became pregnant; that is, females that

1 were spouses or partners of our male patients. In  
2 this group, we have two patients that their spouse or  
3 partner was on Intron/Rebetol, and healthy births we  
4 know about have occurred.

5 We have three on the Intron/placebo, and  
6 one is still blinded. We had four miscarriages in the  
7 Intron/Rebetol group, two miscarriages in the  
8 Intron/placebo group, one miscarriage in a blinded  
9 patient, for a total of seven miscarriages, with four  
10 voluntary terminations, three in the Intron/Rebetol  
11 group, one in the blinded group; and we have ongoing  
12 pregnancies for which we do not have data, a total of  
13 seven in the Intron/Rebetol group, two in the placebo,  
14 for a total of nine.

15 We have five patients at this point in  
16 time that we do not have further data on in the  
17 Intron/Rebetol, one in the Intron/placebo and one in  
18 the blinded group.

19 So in spouses and partners we had a total  
20 of 29 in the Intron/Rebetol group, eight in the  
21 Intron/placebo, and four that are unknown, for a total  
22 of 33. This constitutes the entire population that  
23 was discussed. This includes the controlled trial and  
24 the 25,000 patients in the expanded access.

25 I would make a comment with regard to our

1 discussions with the FDA on labeling for this drug.  
2 This drug will have a very strong pregnancy warning  
3 about the potential for mutagenicity and  
4 teratogenicity, and we will be recommending that all  
5 patients must use adequate contraception for the  
6 duration of the treatment and the duration of the  
7 follow-up, and we are recommending contraception in  
8 both female and male partners, and we will be  
9 indicating that patients should have pregnancy tests -  
10 - female patients -- at least once a month.

11 CHAIRMAN HAMMER: Judith. Dr. Feinberg  
12 who has arrived, thank goodness.

13 DR. FEINBERG: I noted that in the control  
14 group the interferon/placebo group, the response rate  
15 was really very low. Even though the majority of the  
16 patients in this study, somewhere between 60 and 80  
17 percent, depending on the arm, had gotten less than  
18 nine months of interferon therapy previously.

19 I don't know much about how you test for  
20 resistance in hepatitis C, but I'm wondering what  
21 kinds of explorations have been done to look at that  
22 aspect of failure to respond, as that might have some  
23 bearing on the future of the combination as well.

24 DR. ALBRECHT: I think the issue that --  
25 I do not think the response rate is low in the control

1 group, and these are the reasons I believe that that  
2 is correct.

3 If you re-treat patients with the same  
4 dose and regimen to which they previously responded,  
5 the response rate is very low. If you look at the  
6 literature, if we increase the duration of response or  
7 we raise the dose, you can see in relapsed patients  
8 that you will get a better response rate.

9 Accordingly, you get the toxicity --  
10 excuse me, the toxicities that are accorded with the  
11 higher doses and the longer durations.

12 We elected to re-treat the patients with  
13 the same dose and regiment in this study, because that  
14 is the -- actually was the licensed dose and regimen  
15 at the time this study was conducted. So I don't  
16 think the response rate is low from that point of  
17 view.

18 I think what we know about relapsed  
19 patients is, if you raise the dose or increase the  
20 duration, you can proportionally increase the response  
21 rate. However, you cannot achieve the levels that we  
22 achieved with the combination in the 24 week treatment  
23 period.

24 CHAIRMAN HAMMER: Are there other  
25 questions for the FDA reviewers? Dr. Lipsky?

1 DR. LIPSKY: Yes. The information on the  
2 disconcordance of viral response and histology seemed  
3 intriguing. Was further analysis done of that,  
4 besides just asking was there improvement, was there  
5 stability, you know, people who didn't get worse?

6 Then secondly, if you just look at the  
7 situation where the virus seems to have a good  
8 response and there is still a fair number of patients  
9 who histologically do poorly, does that mean we just -  
10 - we're new in understanding what's going on with the  
11 pathogenesis of this disease? What does all this --  
12 Can you make sense of this?

13 DR. NGUYEN: Yes. This is Tan Nguyen from  
14 FDA. The question that you just generated: Actually,  
15 we've given lots of thoughts and consideration to it.  
16 We did some further analysis, and I believe Schering  
17 also did some, regarding the histological improvement,  
18 and is there a connection to the virological response.

19 If you would just simply ignore the  
20 Knodell score and just use a two point indicating  
21 improvement, and less than two indicating no  
22 improvement, if you just simply go in there and plot  
23 out the mean, the distribution of the mean changes  
24 from the baseline of all of the patients, and then you  
25 would say that there is a striking relationship.

1           That is, for those people who -- in the  
2 interferon plus ribavirin treatment arm, for those who  
3 showed evidence of sustained virological response, the  
4 majority of them actually had evidence of histological  
5 improvement, i.e., the distribution of those people  
6 are actually on the negative side of the scale, the  
7 negative meaning better improvement.

8           For those people who did not respond  
9 virologically, did not have sustained virological  
10 response, the majority of them actually did not show  
11 any histological improvement. Actually, some of them  
12 got worse, and very small component of them actually  
13 got better.

14           Now we don't have an explanation for that.  
15 Could that be because of the treatment effect from,  
16 say, interferon? We don't know, but there is a  
17 relationship. That's why we could be comfortable in  
18 making the conclusion that, for those virological  
19 responders, there is a concordance in histological  
20 improvement.

21           DR. LIPSKY: Though your --

22           DR. NGUYEN: Actually, we do have it, yes.  
23 I'm sorry. We do have a slide that we would show the  
24 relationship, but we'll show that. You could say we  
25 have lots of hidden data we didn't present.

1           Let me just stop right here. This is the  
2 -- just one study, 144, which is a U.S. study, and  
3 here we're plotting the mean change from baseline of  
4 the Knodell, and here we use a total score, i.e., the  
5 four components in the histological evaluation.

6           Here we just look at the placebo arm  
7 alone. Well, in the placebo arm we only got like, I  
8 think, about three patients who actually responded  
9 virologically. So we did not plot that thing out,  
10 because it probably would be sort of misleading.

11           If you just look at the rest of them, the  
12 rest of the population in this study arm, you can say  
13 that the mean change in their Knodell score actually  
14 from here to zero, anything negative number is  
15 improvement, you know, positive number is no  
16 improvement.

17           You can see a distribution here. It's  
18 almost like a Gaussian distribution. Actually, some  
19 of them did show improvement, and some of them didn't.  
20 We looked specifically at these people over here,  
21 which show actually a very severe worsening of the  
22 liver biopsy. We did not see any significant  
23 progression in fibrosis in these people.

24           Could you show the next slide, please.  
25 Now this is a slide that I was referring to. Here

1 we're looking at the ribavirin arm of study 144, the  
2 U.S. study. Here I break down the two populations  
3 here, the sustained virological responders and the  
4 nonsustained virological responders in red.

5 You look at the nonsustained virological  
6 responders, you see a distribution of the mean change  
7 in Knodell score from the baseline, actually expanding  
8 from roughly 6 to -7. Probably if you look at the  
9 mean of the mean, it's approximately .7 or .8, which  
10 Schering actually presented that data to you.

11 If you look at the sustained virological  
12 responders indicated by the yellow bar, you can see  
13 actually there is a shift of those yellow bars toward  
14 the positive side, toward the improvement side of the  
15 histological analysis.

16 So this really gives us a degree of  
17 comfort, as I said, that actually histological  
18 improvement is associated with virological  
19 improvement.

20 CHAIRMAN HAMMER: Thank you. Dr.  
21 Pomerantz.

22 DR. POMERANTZ: Yes. I'm going to  
23 continue on this, because I had a similar question  
24 from Dr. Lipsky.

25 If you look at the data that you did

1 provide us but didn't hide on page 6 of at least this  
2 page 6 of the slides here, it is very difficult to  
3 show, looking at that, a clear concordance. You have  
4 in patients who are HCV RNA versus biopsy response in  
5 the combo -- you have 18 percent that have biopsy  
6 improved with no sustained RNA response.

7 If you look in the control group, you have  
8 33 percent with no sustained RNA that still has a  
9 biopsy response.

10 Now that being said, do you think, as  
11 you're alluding to, that the scoring technique that  
12 was used for biopsy evaluation is too sensitive then,  
13 because it seems to be that you're suggesting that  
14 this is a ultra sensitive marker and, if you pull back  
15 on the sensitivity, then you see the difference or a  
16 greater difference. Is that what you're saying?

17 DR. NGUYEN: Well, no. Actually, i did  
18 not go into that type of analysis. On page 6 at the  
19 table that you saw on page 6, when we were looking at  
20 the biopsy improvement over there, we actually used  
21 the applicant's definition of improvement, i.e., an  
22 improvement of two points or greater.

23 Even though it is an arbitrary number,  
24 even though it -- but it does indicate improvement.  
25 However, I think probably the best way to look at

1 histological improvement is not to look at a specific  
2 cutoff, but actually we ought to look at the  
3 distribution of the mean changes from the baseline and  
4 look at it as a total population change rather than a  
5 specific cutoff for each biopsy, and then look at the  
6 -- and then see quantitatively if the biopsy is  
7 actually improved or not.

8 We ought to look at the population base  
9 change for the treatment arms rather than looking at  
10 individual data.

11 Greg, do you have anymore --

12 DR. BEHRMAN: Tan, could I interrupt you.  
13 Another way of paraphrasing that from a regulatory  
14 point of view -- and this gets back to the question of  
15 what are we showing you today that helps you decide  
16 whether or not clinical benefit has been established.  
17 What's the right endpoint?

18 We don't know if two points -- a two point  
19 change is the right endpoint. We could actually ask  
20 you that question. In other words, would another  
21 cutoff be more meaningful? We don't really know that  
22 answer. So it's something we'd like to hear about, if  
23 you would like to see other cutoffs.

24 DR. POMERANTZ: If Dr. Hammer will let me  
25 just go a little farther with this: With the risk of

1 increasing the analogy that's probably overstated in  
2 the literature between human retroviral pathogenesis  
3 and HCV and ways of monitoring it, what we have  
4 learned from human retroviruses is that there are  
5 groups of patients that respond to treatment with  
6 combination therapy that have very little response in  
7 their RNA, and yet their CD4 count may come up.

8           The question is, are we changing this to  
9 a viral strain that is a best fit for that  
10 environment, but not able to cause disease as  
11 proficiently?

12           So one of the things that you could  
13 dissect out of here, if you want to, is whether you  
14 are generating viral strains, as was alluded to  
15 before, that are not as pathogenic, even though you  
16 have no change in the RNA in some of these patients;  
17 because when you use the word sustained, that is  
18 somewhat -- you're giving the virus a lot of time to  
19 make many changes. So you're not able to dissect out  
20 the effect the drug is having.

21           That's why I asked this question, because  
22 changes in the baseline pathology may be in some cases  
23 more relevant than the absolute level of a virus when  
24 it's not looked at clearly for its pathogenic  
25 potential.

1 CHAIRMAN HAMMER: Thank you. We're going  
2 to need to bring this section to a close shortly, but  
3 just a couple of questions, if I may.

4 Did the agency discuss with the sponsor  
5 whether a percentage of these biopsies might be  
6 reviewed by another pathologist? From what I  
7 understood, this was a single pathologist's reading,  
8 and we're looking at RNA, which is the quantified  
9 measure from a laboratory test versus an expert  
10 histologic opinion.

11 Has any of that been done or considered,  
12 particularly as one thinks about moving forward with  
13 this as a paradigm for measurement?

14 DR. BEHRMAN: In terms of the evaluation  
15 of this application, we talked about it initially and  
16 were satisfied that the evaluation they proposed by a  
17 blinded, very qualified individual was sufficient.

18 If you believe there might be utility in  
19 looking at the data in the future, we could certainly  
20 discuss that. Our only prior experience has been with  
21 CMV retinitis where we did not find there was, if you  
22 will, an added value -- We had tried it both ways. We  
23 did not find it was that helpful.

24 CHAIRMAN HAMMER: Just a couple of  
25 clarifications. On the deaths, does the agency and

1 the sponsor agree? In looking at the 23 deaths, there  
2 are a handful that may, one could say, -- are perhaps  
3 probably related, if I'm qualifying that well enough,  
4 to the study treatment, the suicides, the cardiac, and  
5 possibly some of the drug overdoses.

6 It might be good if -- Is it four or seven  
7 cases out of the 23 that seem more likely, if you  
8 will, to be study medication related, because there is  
9 a handful of other deaths that seem pretty unrelated;  
10 and I know it's always difficult in these  
11 circumstances, but there are deaths, and this  
12 committee needs to deal with them, and there are  
13 issues about some of the psychiatric disturbances that  
14 certainly may risk occasional deaths in the future due  
15 to suicide, and we don't fully understand the cardiac  
16 issues, I don't think.

17 Is there relative agreement on the single  
18 digit nature of the more likely relationships?

19 DR. BEHRMAN: Yes. We always are  
20 reluctant to try and establish a single number, and  
21 attribution, as you point out, is very complicated;  
22 but we agree that it's somewhere in that vicinity.

23 CHAIRMAN HAMMER: Okay. One other thing,  
24 just as far as the predictors of outcome, because this  
25 may help future studies as well as clinicians, and

1 you've presented nice data about the early virologic  
2 response in predicting sustained response, and we know  
3 about some of the baseline issues that predict  
4 response, viral load and genotype, etcetera.

5 Was any multivariate modeling done about  
6 early on-study parameters, trying to look at ALT and  
7 RNA or symptom score, whatever, to perhaps help  
8 predict outcome and avoid some of the toxicities in  
9 people who are unlikely to respond?

10 DR. SOON: Yeah. We look at all these  
11 measures separate, because the study, you know, has  
12 limited number of patients. The ALT is also  
13 predictive. That's expected, because ALT and viral  
14 load are correlated pretty well.

15 We also look at them jointly, because with  
16 ALT and viral load it's the predictability mostly due  
17 to the viral load and not due to ALT. And biopsy is  
18 not as predictive as other measures.

19 CHAIRMAN HAMMER: Okay. Just lastly for  
20 the record, it sounds like the FDA analysis is fairly  
21 comfortable with there is a loss to follow-up rate.  
22 There's a loss to follow-up for RNA and a loss to  
23 follow-up for biopsy and some of the missing data  
24 issues were addressed, but it didn't sound like you  
25 were raising any questions about those issues, and it

1 sounds like the agency is comfortable and in  
2 concordance with the sponsor's analysis pretty much.

3 Okay. I'd like to bring -- Well, one more  
4 question. Then we can move on to the open public  
5 hearing.

6 MS. POLLICHINO: I'd like to know in the  
7 patients that relapsed after interferon, did that --  
8 did they have to complete the therapy, respond and  
9 then relapse or did it include any patients that were  
10 PCR negative at 12 weeks and then had breakthrough?

11 MR. FLEISCHER: I'm not sure I understand  
12 what you want to know. Everybody got 24 weeks of  
13 therapy, I believe, irregardless of their time to  
14 response. So I don't --

15 MS. POLLICHINO: When they were on the  
16 interferon alone, I'm saying.

17 MR. FLEISCHER: On the interferon alone?

18 MS. POLLICHINO: Were they included in the  
19 study if they were PCR negative at 12 weeks and then  
20 had breakthrough? Were they included as responders  
21 who then relapsed or did they have to complete  
22 therapy, respond and then relapse?

23 DR. JOLSON: Are you getting at the  
24 definition of what a sustained virologic responder  
25 was?

1 DR. POLLICHINO: Yes.

2 DR. JOLSON: Russ, do you want to clarify  
3 that?

4 MR. FLEISCHER: Well, the original  
5 definition was somebody was considered a virologic --  
6 a sustained virologic responder is they had responded  
7 by the end of the 24 weeks of therapy, meaning that  
8 sometime during that time they had come down to  
9 undetectable, and then they sustained that response  
10 throughout the two measurements that were done at 12  
11 weeks of follow-up and 24 weeks of follow-up.

12 So they came down and stayed down,  
13 basically. If they went down and then blipped up, we  
14 kind of counted those as relapses.

15 CHAIRMAN HAMMER: There will be an  
16 opportunity -- Does that answer you or not? I'm  
17 sorry.

18 MS. POLLICHINO: I'm not quite sure that  
19 that answered the question, unless maybe I didn't  
20 understand.

21 MR. FLEISCHER: All right.

22 MS. POLLICHINO: If a patient was on  
23 interferon, they were PCR negative --

24 MR. FLEISCHER: At what time?

25 MS. POLLICHINO: Twelve weeks.

1 MR. FLEISCHER: Okay.

2 MS. POLLICHINO: But then, say, at seven  
3 months they relapsed. Were those people included in  
4 the combination study or did they have to complete  
5 their --

6 MR. FLEISCHER: Oh, you mean -- No, they  
7 weren't crossed over.

8 MS. POLLICHINO: They were not included?

9 MR. FLEISCHER: No. Either/or, yes, for  
10 randomization. So they got one treatment or the  
11 other, but if they failed or relapsed while on one  
12 therapy, they were not crossed over to the other  
13 therapy.

14 MS. POLLICHINO: Thank you.

15 CHAIRMAN HAMMER: We'll have time for --  
16 Dr. Jolson? Did you have a comment?

17 DR. JOLSON: Yes. I just had one comment,  
18 getting back to some of the questions pertaining to  
19 the biopsy data. One thing that might be helpful for  
20 the committee -- I know you've requested to review a  
21 few of the slides. It might be helpful to reiterate  
22 some of the issues pertaining to liver biopsies and  
23 their interpretation, and some of the limitations as  
24 far as sampling might be helpful just to provide some  
25 context for the data.

1 CHAIRMAN HAMMER: Thank you. There will  
2 be more time for discussion and questions to the  
3 sponsor and the agency after lunch, but trying to keep  
4 us on schedule or relatively so, the next portion of  
5 the agenda is the open public hearing.

6 There are two people who have signed up to  
7 speak, and one letter that's been submitted, and there  
8 may be other people who want to volunteer.

9 The first person is Vinod Rustgi, a  
10 hepatologist who is medical director of liver  
11 transplantation at Georgetown University School of  
12 Medicine. Dr. Rustgi, please come to the podium.  
13 Also, please, for any of the speakers, disclosure is  
14 important during this phase.

15 DR. RUSTGI: Thank you. My name is Vinod  
16 Rustgi. I am, as you stated, medical director of  
17 liver transplantation at Georgetown.

18 We did conduct or participate in this  
19 combination therapy while at Inova, Fairfax Hospital.  
20 This funding was provided by Schering-Plough, and I  
21 have participated in other clinical trials with  
22 funding from Schering-Plough, and I do have some stock  
23 in Schering-Plough as well.

24 We have been using the only available  
25 treatment for chronic hepatitis C, interferon, since

1 1990, and as the committee realizes, unfortunately, it  
2 doesn't work for many of our patients.

3 The lack of a truly effective treatment  
4 for hepatitis C has been very frustrating for both  
5 physicians and their patients. Patients, obviously,  
6 want to improve and, no matter how carefully they are  
7 counseled about the likelihood of nonresponse or  
8 relapse, they think they will be among those lucky few  
9 who clear the virus permanently.

10 The data from the trials shows that  
11 combination therapy increases response rates, as you  
12 have seen, especially in those who have relapsed after  
13 a course of interferon monotherapy. This is a major  
14 advance in what we can offer these patients.

15 We found that the side effects of the  
16 combination therapy were tolerable. They were still  
17 there, but relatively easy for the patients to get  
18 through, and that this was an easy course of therapy  
19 to administer.

20 As a transplant physician, we see patients  
21 arriving weekly, daily with end stage liver disease.  
22 Liver failure due to hepatitis C is the leading  
23 indication for liver transplantation in this country.

24 As you know, there are not enough organs  
25 available for transplantation in the United States.

1 There are more than 10,000 people on the waiting list  
2 for liver transplant, and last year there were about  
3 2700 liver transplantations done.

4 Now everybody is in critical need who is  
5 on the waiting list, but the demand clearly outweighs  
6 the supply. This underscores the need for effective  
7 treatment for hepatitis C and, if we can combat the  
8 disease before it produces end stage cirrhosis, we  
9 could greatly reduce the number of people needing  
10 liver transplantation.

11 From the perspective of my patients who  
12 have participated in this trial, I can tell you that  
13 they felt lucky to be offered combination therapy.  
14 They were motivated, positive people who wanted to get  
15 better.

16 It is difficult to tell them after a first  
17 course of therapy that they have relapsed, but when we  
18 approached them about combination therapy, they were  
19 enthusiastic to try it.

20 The data show that the combination therapy  
21 works, and it's my hope that the committee delivers a  
22 positive recommendation today, beginning to fulfill  
23 the need for better and more effective treatments for  
24 people with chronic hepatitis C.

25 CHAIRMAN HAMMER: Thank you. The next

1 speaker signed up as Mary Ianelli to give us a patient  
2 perspective.

3 MS. IANELLI: Yes. My name is Mary  
4 Ianelli, and at this time I would like to state that  
5 I have not received any financial gain from anyone  
6 during the study up to this point.

7 I'd just like to tell you about my  
8 experiences with the hepatitis C and the availability  
9 and the treatment, the combination therapy which has  
10 made me virus free at this time.

11 I'm a wife and a veterinarian's assistant  
12 in Burke, Virginia, and almost as important to me as  
13 my husband and my profession is the fact that I am a  
14 former hepatitis C patient.

15 The story begins with about eight years  
16 ago I was a Fairfax County firefighter and emergency  
17 medical technician. I was participating off duty at  
18 the Laurel Racetrack as an EMT when a track worker was  
19 kicked by a horse.

20 Even though I wasn't working as the  
21 responding EMT at that time, I was the first on the  
22 scene, and that's when I actually think I was exposed  
23 to the hepatitis C virus.

24 Blood from the person who had been kicked  
25 by the horse came in contact with an open wound that

1 I had at the time. To the best of my recollection,  
2 that's when I think I received the hepatitis C virus.

3 I first learned that I had the hepatitis  
4 C virus a few years ago. I had gone to -- A new  
5 gynecologist I was seeing conducted a full blood  
6 screen. The liver enzyme levels came back unusually  
7 high. She referred me to my regular internist. He  
8 confirmed hepatitis C, and then referred me to a  
9 specialist.

10 I was in shock when I found out about the  
11 hepatitis C. A previous blood test had shown high  
12 enzyme levels, but my doctor at the time said to  
13 disregard this because of all the exercising and  
14 running I used to do, and that was a possibility of  
15 causing this.

16 Six weeks after I visited the specialist,  
17 I began taking interferon. In the beginning, I had  
18 all the side effects, the flu-like symptoms, the achy  
19 joints and nausea, but I never missed any time off  
20 from work. Six month later, my enzyme levels were  
21 back to normal.

22 I was thrilled, but then a month later  
23 they were back up again. I was very disappointed when  
24 my doctor told me that the infection had returned,  
25 because I had undergone treatment with this, and it

1 was a very draining medication. I had had two liver  
2 biopsies, but I was determined to fight this.

3 My doctor told me that I could try  
4 interferon over a longer period of time or at a higher  
5 dose, and I was willing to try this; but I was very  
6 concerned about the damage that I had received to my  
7 liver.

8 Then I learned about the combination  
9 therapy, and I was told by my doctor that he thought  
10 that it would help. I would be more than happy to try  
11 it. About 18 months ago, I started another six months  
12 of treatment with the combination therapy. I had the  
13 same side effects as before, but I'm very happy to say  
14 that I am virus free for nearly 12 months after I  
15 stopped taking the medication of the combination  
16 therapy.

17 It has done a wonderful thing for me, and  
18 I don't have to worry about affecting anyone if I cut  
19 myself, and it makes me very worry free.

20 I would just like the time to say to the  
21 panel and the members and anybody that has hepatitis  
22 C should have this opportunity to try the combination  
23 of drugs.

24 Thank you very much.

25 CHAIRMAN HAMMER: Thank you very much.

1           Is there anyone else here who wishes to  
2 come to the microphone as part of the public session?  
3 If not, we have a relatively brief letter submitted by  
4 Dr. Thomas Majarian from Belmont, Massachusetts, and  
5 I'll just read this into the record.

6           "I support the addition of ribavirin with  
7 interferon alfa-2b for treatment of chronic hepatitis  
8 C. Ribavirin is relatively easy to use and has side  
9 effects which are substantially less than interferon.

10           "Hemolytic anemia is usually recognized  
11 and treated with temporary dose reduction. There is  
12 one aspect of the approval package that I believe is  
13 being requested by Schering-Plough that I would like  
14 to strong recommend to the committee that they do not  
15 endorse.

16           "It is my understanding that Schering-  
17 Plough would like ribavirin to be packaged together  
18 with Intron A, so that the only way for a physician to  
19 prescribe ribavirin would be to also prescribe Intron  
20 A at a fixed dose for both drugs.

21           "As a physician with clinical experience  
22 treating hepatitis C patients, it is my belief that  
23 providing these two drugs in a fixed dose package  
24 would likely lead to increased medical costs, because  
25 the dosage of both drugs must be altered often, due to

1 side effects of the medications.

2 "For example, some patients might require  
3 lower doses of ribavirin due to hemolytic anemia,  
4 while maintaining their regular dose of interferon.  
5 Other patients might require a dose reduction of  
6 interferon due to low WBC or platelet counts, while  
7 continuing on full dose ribavirin.

8 "If a fixed dose combination of medication  
9 such as Bactrim or Septra is generally the correct  
10 dose for most patients, especially when both  
11 medications are in the oral form, thus reducing the  
12 number of pills to be taken for a given condition,  
13 then I would agree that this makes sense.

14 "When two medications are to be given by  
15 different routes, as with Intron A and ribavirin,  
16 especially when both medications have common but  
17 different side effects that require dose adjustment,  
18 it makes no sense to package them together.

19 "This might also mislead doctors who are  
20 unfamiliar with the drugs to assume incorrectly that  
21 the dosage packaged can be used for all patients with  
22 hepatitis C without regard to monitoring for possible  
23 dose adjustments.

24 "Thank you for your time and  
25 consideration."

1                   Again, that's from a Dr. Thomas Najarian  
2                   at Belmont, Massachusetts.

3                   Thank you. That brings to a close the  
4                   open public discussion, and we are on schedule for  
5                   lunch. We will reconvene here at 1:00 p.m. sharp.  
6                   Thank you.

7                   (Whereupon, the foregoing matter went off  
8                   the record at 11:49 a.m.)

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## A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:03 p.m.)

CHAIRMAN HAMMER: Would you please take your seats. We're going to start in a minute or so.

I'd like to reconvene this meeting and open the afternoon session. I'd like to start by just mentioning for the record that the letter I read from Dr. Najarian in Massachusetts did not come with a disclosure statement. So we will be formally requesting one and put it into the record.

Now what I'd like to do for the first part of the afternoon -- The agenda has four hours listed for open committee discussion. I don't think we'll necessarily need all four hours, and certainly, if we do, there will be a break scheduled in the midst of that.

What I'd like to do to open this before we go to the questions that are being put before us by the agency is to give a little bit more time for the committee members to flesh out any issues or questions from the sponsor, but I would also like to open the afternoon with the offer and our request to perhaps see a brief review of some of the pathology slides. That would be quite informative.

Please announce yourself for the --

1 Identify yourself for the record.

2 DR. GOODMAN: My name is Zachary Goodman.  
3 I'm the Chief of the Hepatic Pathology Division of the  
4 Armed Forces Institute of Pathology, and I'm also the  
5 blind pathologist who read all of the slides from the  
6 study.

7 CHAIRMAN HAMMER: Blinded pathologist.

8 DR. GOODMAN: Yes. That was meant to be  
9 a joke.

10 May we put on slide 60 while I'm giving a  
11 little preliminary information. This is probably not  
12 legible, but this is what we're talking about with the  
13 Knodell score. This is a scoring system that was  
14 devised in the late 1970s by Dr. Robert Knodell, who  
15 is a gastroenterologist, and my colleague, Kamal Ishak  
16 who is a pathologist.

17 Between the two of them, they came up with  
18 this scoring system, because they were planning a  
19 multi-center study for evaluation of treatment of  
20 chronic non-A/non-B hepatitis.

21 In the 1970s it really wasn't clear how  
22 many diseases constituted non-A/non-B hepatitis, and  
23 now we know mostly that's two diseases. There's  
24 autoimmune hepatitis, which is a very severe disease,  
25 and there's hepatitis C, which tends to be a mild to

1 moderate smoldering disease; but they made up this  
2 scoring system that would cover all of the bases.

3           What Dr. Ishak did was he recognized that  
4 there are different histologic features that you look  
5 at to come up with an impression of what a biopsy has.  
6 You look at the portal inflammation, which is the  
7 Knodell category 3. You look at the amount of  
8 interlobular -- that is, the acinar injury, the  
9 injury to the liver cells all over the liver; and then  
10 we also look very critically at the area where the  
11 portal areas meet the surrounding liver tissue. That  
12 goes by the name of the limiting plate, and that's  
13 what we talk about, a periportal injury.

14           Now you recognize that you could grade all  
15 of these. Sometimes they're mild. Sometimes they're  
16 moderate. Sometimes they're severe, and they can come  
17 in just about any combination.

18           Then there's also the fibrosis, which  
19 relates to the stage of the disease. The activity is  
20 the first three categories.

21           Now down at the bottom here, the first  
22 category goes from zero to ten, and that's because in  
23 autoimmune hepatitis very often you will have really  
24 severe injury with confluent necrosis of large areas  
25 of the liver and, depending on how much there is, you

1 get five, six or ten points when you've got that, as  
2 opposed to the maximum of four if you don't have that.

3           Once in a great while, you'll see one of  
4 these in viral hepatitis, but it's extraordinarily  
5 rare. For viral hepatitis really, this first  
6 category, category 1, for most purposes stops at four.  
7 We have a couple of them that got as high as six, but  
8 mostly it stops at four.

9           So the maximum score isn't really 18.  
10 It's really 12, for most purposes.

11           Now I want to say something a little bit  
12 about variation in biopsies and why you might see some  
13 improvement, even when you don't think you have some  
14 response.

15           One reason is because of the natural  
16 history of the disease. We know that hepatitis C is  
17 a disease that waxes and wanes, and sometimes the ALT  
18 will go very high. Sometimes it will go very low,  
19 come back to normal, even when the patient is  
20 asymptomatic under both conditions.

21           If you do a liver biopsy when the ALT is  
22 very high, there will be a lot more inflammation and  
23 injury than when it's very low. So these are protocol  
24 biopsies. They're not done for a purpose -- for an  
25 indication. So the natural history of the disease

1 could just make the biopsy improve or worsen on its  
2 own.

3           Sampling is also a problem. The liver  
4 weighs about 1500 grams and, when you do a liver  
5 biopsy, you're getting about 15 milligrams of tissue.  
6 That's like 1/100,000 of the liver that we're  
7 sampling. I can show you liver biopsies that are a  
8 couple of centimeters long in which one end of the  
9 biopsy will look very bad, and the other end will look  
10 fairly mild. Hepatitis is a patchy disease. It  
11 doesn't affect the whole liver evenly throughout every  
12 millimeter of tissue.

13           So if you have a small biopsy, it could  
14 miss the area that has a lot of inflammation, or it  
15 could hit the area that has a lot of inflammation, and  
16 that will affect the final score.

17           Now then there's also differences in the  
18 reading. Now you notice you get a score of 1 if you  
19 have mild, and you get a score of 3 if it's moderate.  
20 You know, sometimes you can have a change of less than  
21 one category, but you can go from the low end of  
22 moderate to the high end of moderate.

23           There might be a great deal of difference  
24 in inflammation, or if you go from the high end of  
25 mild to the low end of moderate, there may not be very

1 much difference at all, but that changes the score.  
2 Every study that's ever been done looking at inter-  
3 and intraobserver variation has noted this, that  
4 sometimes when the same pathologist reads the same  
5 slides on a different day, he'll score them a bit  
6 differently.

7 The only around this is to use the  
8 statistical -- the power of statistics. You have to  
9 have enough patients that these differences will  
10 average themselves out.

11 One other thing I want to mention is about  
12 how can you have a sustained response in some patients  
13 who are getting interferon, and I'll come back to that  
14 in a minute.

15 Now this is too small to read, but just I  
16 want to show you. You get a certain number of points  
17 for mild in each category, moderate in each category,  
18 and severe in each category. So let me show some  
19 examples of these quickly.

20 I want to go to the histologic slides.  
21 There we go. Turn the projector off. Just to review  
22 for those of you who are not pathologists, here's a  
23 portal area from a normal liver. Every normal portal  
24 area has a portal vein branch, which is this large  
25 structure here. It has an hepatic artery, and it has

1 a bile duct, and it doesn't have very many  
2 inflammatory cells. You may find a lymphocyte if you  
3 look real hard, but really no inflammation, and  
4 there's very little fibrous supporting stroma. That's  
5 normal.

6 Now here's from one of the patients in the  
7 study. You can see there's a portal area over here.  
8 Over here we have the parenchyma, and right at the  
9 interface between the parenchyma and the portal  
10 connective tissue there's an acidophilic body right  
11 here. That's the dying hepatocyte, a liver cell  
12 that's undergoing apoptosis and in the process of  
13 dying.

14 This was a post-treatment biopsy, but the  
15 patient didn't really have a histologic response or a  
16 virologic response, but even so, all we have is this  
17 one little focus of injury right here. So if that's  
18 all we have, then we would grade that as mild.

19 Now the hooker is that you have to look at  
20 all of the portal areas. You can't just look at one.  
21 We have to look at all of them, and average them out.  
22 So one might be mild. Another might be moderate, and  
23 another might be severe, and we have to come to a  
24 conclusion. That's one of the sources of variation in  
25 the reading.

1 Here's another one. This patient has a  
2 moderate amount of portal inflammation and also has  
3 some injury to the periportal area. The lymphocytes  
4 are leaving the portal area and going out into the  
5 surrounding tissue.

6 That's the lesion that we refer to as  
7 interface hepatitis or piecemeal necrosis, and  
8 traditionally now for 30 years, that's been thought to  
9 be probably the most significant lesion in chronic  
10 hepatitis, is the injury to the tissue surrounding the  
11 portal areas.

12 The name piecemeal necrosis was coined by  
13 Hans Paper in the early 1960s, because he did some  
14 studies showing that there's immunoglobulin associated  
15 with this type of injury, and he thought that this was  
16 the immunologically mediated injury that is the  
17 significant and progressive form of liver disease  
18 which occurs in chronic hepatitis.

19 We now know that most of the injury is  
20 done by T cells in this area, but that's still  
21 something that we can recognize, and in grading the  
22 biopsy you look at, you know, what percentage of the  
23 circumference is involved with this interface  
24 hepatitis.

25 We don't have any over here, but we have

1 some over here. So less than half of the portal area  
2 -- of the circumference is involved in those portal  
3 areas. We would call it moderate. That one is  
4 moderate.

5 Here's one that's got a little more portal  
6 inflammation, but also has a moderate amount of  
7 piecemeal necrosis. So in category 1 that gets scored  
8 as a 3.

9 Here's one that's a lot more severe.  
10 There's a lot of portal inflammation here. So the  
11 portal inflammation we would score as marked. So we  
12 score that as 4, and the interface hepatitis goes all  
13 the way around. There's no discrete limiting plate,  
14 because the lymphocytes are all migrating out and  
15 causing damage to the surrounding liver tissue and  
16 causing the portal area to expand. That would get a  
17 score of 4.

18 The other component -- Another component  
19 of the injury is the parenchymal injury, and this is  
20 very difficult to show in photo mics, because you have  
21 to look at the whole thing and get an idea of how much  
22 there is.

23 If we look at -- Here's one. A little  
24 focus was a cluster of inflammatory cells. That marks  
25 the site of liver cell dropout. If there's only one

1 or two of those in a high power field up to a maximum  
2 of 4, then that's mild. If there's a lot of them,  
3 like we have here, it would be -- if we have five to  
4 20 of these clusters of inflammatory cells showing  
5 there's been loss of liver cells, then we would call  
6 that moderate and, if there's more than 20, we call it  
7 marked. But you have to average out the whole  
8 specimen, and again on different days it might look  
9 mild or it might look moderate.

10 So let me show you a couple of pre and  
11 post treatment biopsies to show some improvement.  
12 Here's a pretreatment biopsy from this patient. This  
13 is of one portal area. There are lots of portal  
14 areas, of course. So we have to look at all of them,  
15 but we can see that there's interface hepatitis going  
16 all the way around.

17 That means there's quite a bit of  
18 periportal injury. That would get a score of 4.  
19 Here's the same patient after treatment, one of the  
20 portal areas. It has no inflammation and no piecemeal  
21 necrosis, but it does have - It's enlarged. It's got  
22 some fibrosis. So he's left with some residual  
23 fibrosis to show that he had disease there in the  
24 past.

25 I could -- I will tell you, those really

1 did come from pre and post treatment biopsies, but  
2 sometimes you can find those same looking portal areas  
3 in the same biopsy. So you have to look at the whole  
4 specimen and average it out.

5 Here's another one. This pretreatment  
6 biopsy shows a tremendous amount of periportal injury,  
7 and the same patient post treatment. Here's a portal  
8 area up here, and there's no inflammation or  
9 periportal injuries. There's quite a bit of  
10 improvement in that case.

11 Here's looking -- The same thing happens,  
12 looking at the parenchymal injury. Here's a  
13 pretreatment biopsy showing some apoptotic cells here  
14 undergoing degeneration, surrounded by lymphocytes;  
15 and here's the same patient post treatment showing  
16 normal liver cell plates. We, of course, have to look  
17 at the whole specimen, but if they all look like that,  
18 then we would consider it improved.

19 Here's a patient that didn't improve.  
20 Here's his pretreatment biopsy showing a great deal of  
21 periportal injury and also spotty necrosis out in the  
22 parenchyma. Here's the same patient post treatment,  
23 showing the same amount of periportal injury.

24 Could I have slide 64, please. So I'll  
25 just emphasize, you know, what we have to do then is

1 look at all of them and average out what we're dealing  
2 with, and then summarize it and come to some sort of  
3 meaningful interpretation of what's happened to the  
4 whole population, not to each individual patient.

5 The best way to do that, I think, is to  
6 average the Knodell scores. So this is similar to  
7 what you've seen previously. Here's the United States  
8 studies and the international studies.

9 The patients who were sustained responders  
10 getting both the combination of Intron A and Rebetol  
11 had an average decrease in histologic score of four.  
12 Those who did not have a sustained response still had  
13 an improvement of only .7.

14 The same thing is true with the ones who  
15 got the placebo. There weren't very many of them but  
16 they had a marked improvement. Those who did not have  
17 a sustained response still had an improvement.

18 Why is this? Well, we know that that's  
19 what happens with interferon. Interferon is effective  
20 in some ways, even if it doesn't completely eradicate  
21 the virus. We know that it causes the ALT levels to  
22 decrease, and we know that at least in some patients  
23 it causes improvement in the histology. It decreases  
24 the amount of inflammation and injury.

25 Could I have slide 72. Perhaps we should

1 look at it another way also. You know, what would it  
2 take to actually cure the patient? Well, you would  
3 want to eradicate the infection and bring the liver  
4 back to normal or close to normal.

5 So I think a normal liver biopsy could  
6 have a little bit of inflammation, particularly  
7 somebody who has had hepatitis and has recovered.  
8 There may still be a little bit of portal  
9 inflammation, a little bit of piecemeal necrosis and  
10 an occasional cell that's dying out within the  
11 parenchyma.

12 That would get a score, say, of 3 and, if  
13 there's less than that, it would be 2 or zero. So if  
14 you had a score of zero to 3, I think your liver  
15 biopsy is either normal or close to normal. So if we  
16 look at all of the patients in the study that we had  
17 paired biopsies on, those who got placebo -- there  
18 were only 2.2 percent of patients who would meet that  
19 criteria for a cure. I'll put the "cure" in quotation  
20 marks. We don't know that he's really cured, but he  
21 would, to all appearances, appear cured at that point  
22 in time. 2.2 percent would meet that criterion.

23 If you look at the ones who got interferon  
24 and ribavirin, there's about 46 percent who had normal  
25 or nearly normal liver biopsies by that criterion, and

1 also sustained loss of hepatitis C RNA. That's 46  
2 percent. So that's not a tenfold improvement. That's  
3 actually a twentyfold improvement over the placebo.

4 So that's all I have to say. Thank you.

5 CHAIRMAN HAMMER: Thank you very much.

6 Could we have the lights on.

7 I'd like to give the committee members now  
8 an opportunity to bring up points of discussion or  
9 questions. Dr. Lipsky.

10 DR. LIPSKY: Yes. On your presentation,  
11 is it an assumption to say that there must be ongoing  
12 infection with a virus to have abnormal, you know,  
13 pathology? Do we understand -- because it seems like  
14 we're relatively new enough in detecting the virus.  
15 Do we know, could the virus trigger an immunologic  
16 response, the virus be gone but the response live on  
17 after the virus is gone? Is that a possibility or is  
18 that known to be certainly not?

19 DR. GOODMAN: That's always been suspected  
20 as the cause of autoimmune hepatitis, that some  
21 patients get a viral infection and then that triggers  
22 the autoimmune hepatitis, really severe hepatitis  
23 that's ongoing.

24 I think most patients with hepatitis C do  
25 not have that. They have relatively mild disease

1 which must be related to viral replication. I think  
2 we've shown that here with these studies.

3 DR. LIPSKY: Well, have we?

4 DR. GOODMAN: Well, if --

5 DR. LIPSKY: And have you looked at -- I  
6 realize that you were blinded, but have you looked at  
7 those who did not improve but yet were -- you could  
8 not detect the virus, at least at the level of  
9 detection. We realize that now with HIV they are  
10 supersensitive to assays that detect way down, and one  
11 could, you know, make -- I don't know what the level  
12 of detection is, you know, on the current assays, but  
13 is there anything special about those biopsies in  
14 those people who were "cured," at least of the virus?

15 DR. GOODMAN: A lot of them still had  
16 fairly low histologic scores. It would have been 4  
17 and 5, and I think, given time, some of them will  
18 probably come back to normal as well.

19 There's still a few others that we haven't  
20 had a chance to look at that had either worse or still  
21 significant amounts of disease, but I'm not really  
22 sure if there's anything special about them.

23 DR. GRETCH: Can I make a comment as a  
24 virologist? We've published an experience from  
25 Seattle, the University of Washington, using highly

1 sensitive PCR tests to monitor therapy, actually have  
2 written several papers, to look at -- with the  
3 assumption that we took several years ago that  
4 hepatitis C might be a viral disease.

5           Trying to demonstrate this, we developed  
6 the most sensitive assays we could for viremia and  
7 viral eradication. In our studies we found that  
8 individuals who were negative for virus after therapy  
9 was completed and remained there one month out or six  
10 months out, if you have the hypothesis that there  
11 might still be viral replication going on, we would  
12 think that long term the virus would reappear and  
13 disease would; but, in fact, we found no evidence of  
14 that, and we found no evidence of it in lymphocytes or  
15 liver biopsies in a very careful study.

16           On the other hand, we found that patients  
17 that were going to relapse clinically or virologically  
18 did so very rapidly within one month, and they had  
19 typically very high viral loads, ten to a hundred  
20 times higher than the average HIV infected patient.

21           So this appears to, in the setting of  
22 therapy, not be a case -- in our laboratory and in  
23 several other laboratories that have done careful  
24 studies a case of a smoldering virus after you stop  
25 therapy.

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1           There are exceptions. It's less than ten  
2 percent. It's about five percent of patients, you  
3 will find a pattern of -- we can't detect the virus in  
4 the serum. We can't detect it in the liver, but  
5 there's abnormal liver enzymes.

6           We don't know what's going on, and we  
7 suspect that maybe we've triggered -- with therapy or  
8 with the long term viral infection, there may be an  
9 autoimmune component. But this is a very unusual  
10 event, and I make this statement, because you have a  
11 very intelligent question, and I think there is  
12 controversy in the literature, but at some point we  
13 have to have some faith that we do have some accurate  
14 markers and that some of the research being performed  
15 is believable.

16           I didn't do the virology work for the  
17 current study, but I have inspected the laboratory  
18 that's done it. I know the FDA has actually approved  
19 that laboratory for screening blood products for RNA  
20 for hepatitis C, and I believe that that laboratory is  
21 able to document eradication of virus after therapy  
22 and that the sustained eradication out to six months,  
23 I believe, will be highly predictive of a sustained  
24 response.

25           In Seattle, we think of it as an RNA

1 virus, that there's a likelihood of a cure here,  
2 because it's not a DNA virus. There's not  
3 integration. We don't know of RNA viruses that  
4 disappear long term and reappear. That certainly  
5 could be the case, and that that's happened at low  
6 frequency with sustained responses in hepatitis C.

7 If you look at the four/five, your follow-  
8 up data, there are patients where you see reoccurrence  
9 of virus, but we don't know if those patients have  
10 become reinfected due to risk -- continued risk,  
11 exposure, high risk exposure, etcetera.

12 So from all perspectives, that's -- the  
13 virology perspective, this looks like, when you  
14 eliminate the virus from the blood and it's sustained  
15 after treatment is stopped, we're in a sustained  
16 remission, and I think all of the good data in the  
17 field would support that.

18 I'm happy to hear other people's comments  
19 on that, but I feel that's important to make that  
20 strong statement to the FDA.

21 DR. EL-SADR: I have a question regarding  
22 the pathology. Is the choice of greater than or equal  
23 to two steps or points as a criterion for response --  
24 is that established? I mean, is that something that's  
25 -- I mean, why were two points picked?

1 DR. GOODMAN: Well, I wasn't the one who  
2 picked them. I think that was decided between  
3 Schering and their conversations with the FDA, that  
4 that would be a reasonable amount of improvement.

5 I think, when you're dealing with an  
6 individual case, you can't be sure, because of  
7 variations in the disease, variations in the reading  
8 and variations in sampling. If you're dealing with a  
9 population, then you can say, yes, perhaps an average  
10 score of two is very significant or --

11 DR. EL-SADR: That's an average change of  
12 two.

13 DR. GOODMAN: Yes, average change of two,  
14 average decrease in the score of two. I think they  
15 actually proved it the hardest way, by showing that  
16 there were more patients who had a change in two. If  
17 you look at any other way of looking at the data, I  
18 think it looks a lot better than that.

19 DR. EL-SADR: I mean, the reason I'm  
20 thinking about that is in the placebo arm the 33  
21 percent of the group had biopsy improvement as --

22 DR. GOODMAN: But we know that happens  
23 with --

24 DR. EL-SADR: -- as per the criteria that  
25 I just mentioned, and few of them had -- and no

1 virologic response. So I'm wondering, is it possible  
2 to have used the higher cutoff of more points?

3 DR. GOODMAN: Yes, I think it would have  
4 made the differences look more dramatic if they had,  
5 but you know, it is true that interferon alone will  
6 cause improvement in the liver biopsy inflammation.  
7 That was shown in the initial studies when the drug  
8 was approved.

9 DR. EL-SADR: So you think the effect of  
10 the ribavirin is mainly on the -- What I'm getting at  
11 is it looks like the interferon effect is somehow on  
12 the biopsy changes, and that the ribavirin is adding  
13 more of the virologic response. Is that --

14 DR. GOODMAN: Seems reasonable to me.

15 DR. HAMILTON: Correct me if I'm wrong,  
16 but I don't think we've been presented today with much  
17 in the way of objective evidence about the virologic  
18 response in the liver per se. We've just heard a  
19 somewhat, I think, positive report -- I'm sorry, I  
20 don't know your name, and I'm on this committee, but  
21 I'd like to know by what techniques you've  
22 demonstrated the absence of virus in the liver pre or  
23 post treatment, and because I think the principle is  
24 true, that absence of detection is not detection of  
25 absence.

1                   So maybe you could elaborate, if you  
2 would, please. Were these immunohistochemical tests?  
3 Were these in situ hybridizations? Were they in situ  
4 PCR? What were they?

5                   DR. ALBRECHT: I'm sorry. I didn't  
6 understand which tests you're referring to.

7                   DR. HAMILTON: I was talking to the ones  
8 that he --

9                   DR. GRETCH: I'll certainly address that.  
10 We've done a fair amount of work optimizing for  
11 sensitivity, and we have a sensitivity for RNA  
12 detection in liver biopsies of less than 100 copies  
13 per biopsy specimen, and we're able to show that in  
14 the typical biopsy specimen there's  $10^8$ ,  $10^9$  genome  
15 equivalence of RNA in a patient with untreated  
16 hepatitis C, and we were able to show in patients who  
17 were responders to correlate with sustained response  
18 biopsies done after therapy that there was no  
19 detectable virus at a sensitivity level of less than  
20 100 copies per --

21                   We also did the study in white blood cells  
22 in addition to liver. Now certainly, I would agree  
23 with your point that -- and I think the point that  
24 absence of detection does not mean detection of  
25 absence, but what I'm arguing, to try to help you

1 understand the biology, is -- the biology is when you  
2 stop therapy, it's an -- When we look at it  
3 objectively, it's like an -- The virus either come  
4 storming back or -- the observations from the  
5 interferon trials -- or it doesn't for a long period  
6 of time. For up to five years now, the studies have  
7 been conducted.

8 That doesn't mean forever, and this is  
9 just one piece of evidence, but I just want to share  
10 with you the virology perspective, that when you stop  
11 therapy in these patients, when those patients  
12 relapse, there's lots of virus being made very, very  
13 fast.

14 It's like we have an aggressive antiviral  
15 keeping it down, and it comes back very, very fast.  
16 When these break through, we see a big change in the  
17 viral quasi-species. There's a whole new variant  
18 population there, and there's a rapid increase in  
19 viremia.

20 So these drugs look very much like direct  
21 antivirals in nonresponders. They change to quasi  
22 species at a very high rate, higher than untreated  
23 controls. We've published that in Journal of Virology  
24 this month, and I think this is not objective evidence  
25 in the patients per se, but what I'm trying to share

1 with you -- I believe I was invited here to help you  
2 understand the virologic basis of this disease.

3 I believe that Michael Houghton's  
4 discovery in '89 of the viral agent and the discovery  
5 of the antibody test -- if you look at it, you know,  
6 four to 5 million people infected now with the virus  
7 marker. I mean, it's very clearly established that  
8 this liver disease is caused by hepatitis C.

9 I think this study -- It's very important  
10 that the FDA realize that there's some very objective  
11 data in this study correlating eradication with  
12 improvement in histology, as I've seen the data. It  
13 looks like a significant correlation between patients  
14 who are sustained virologic responders and improving -  
15 - in serum and improvement in histology, as I saw the  
16 data.

17 DR. HAMILTON: I guess you would agree  
18 that you would like to see the data on the liver  
19 itself with respect to virus.

20 DR. GRETCH: Certainly, I would like to  
21 see it, but you can't do everything in one step. You  
22 know, this is a very, very important disease with 4  
23 million people infected and people dying every day,  
24 and we have to sometimes take baby steps with  
25 difficult problems.

1           So I think we can't overlook the  
2 achievements of this study. I think we have to be a  
3 little bit balanced in what our expectations are from  
4 these studies as we go forward.

5           CHAIRMAN HAMMER: Please go ahead.

6           DR. LIPSKY: Would you comment on the  
7 observation that it looks like, if you develop a  
8 undetectable virus after the -- I think it was the 12  
9 week period -- that was less likely to be sustained  
10 than those who did it early on. Based on your  
11 background, do you have any explanation for that  
12 phenomenon?

13          DR. GRETCH: I think that's a wonderful  
14 question, and we're getting again defending the  
15 position that this is an antiviral -- this is the  
16 right committee to address these drugs. This is  
17 perfectly consistent with what we saw in our Phase II  
18 dose finding studies, pharmacodynamic studies,  
19 recently published in Hepatology.

20          There's a significant dose effect with  
21 interferon in nonresponder patients with high viral  
22 loads and genotype 1. If you give more drug, there's  
23 a more rapid slope. It's just like HIV.

24          Talk to Alan Perlson who modeled all of  
25 David Ho's stuff. Looks just like it. There's a

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1 direct correlation with monotherapy. The sooner you  
2 get rid of the virus, the more likely you respond. If  
3 it's slower, you probably need to treat longer.

4 I think the data at four weeks and 12  
5 weeks argues that ribavirin, albeit we don't know what  
6 it's doing, it's probably just being a wimpy  
7 antiviral, like we know it has been, but it's doing  
8 something.

9 The clinical data is telling us something,  
10 that in combination in these retreatments it's  
11 certainly having an effect. And I guess my reputation  
12 is nothing. I can go on line and say I'm going to  
13 predict that these patients are going to have a  
14 tremendous benefit, and I think that there's other  
15 people out there that deserve a chance at being  
16 treated with this drug.

17 DR. LIPSKY: But I'm just -- You know, to  
18 the question, we have -- Can you be more precise  
19 exactly what you think is going on. In other words,  
20 someone at week 20, they say, ah, it's wonderful.

21 DR. GRETCH: What's going on. I think  
22 we're below -- There's probably -- and if we look at  
23 the modeling of our most recent interferon alone  
24 dosing studies, there's a two-phase kinetic  
25 elimination.

1           There's a rapid first phase, and it occurs  
2 very rapidly the first couple of weeks, within 14 days  
3 it's done. Then there's a second elimination phase  
4 that's a lot slower. We don't know why there's a  
5 second phase, but it's over 100 to a thousandfold  
6 reduction in virus sometimes within two doses.

7           It's a very rapid knockdown, but not a  
8 knockout in these patients.

9           DR. LIPSKY: So you would argue that we  
10 should -- one should restart a clock on those people  
11 as soon as they become undetectable and have a certain  
12 duration of therapy thereafter?

13          DR. GRETCH: A clinical trial, I think,  
14 would be warranted to ask is there a sort of -- once  
15 a patient is eliminated, is there a duration of  
16 therapy we should give them to sort of improve the  
17 chance of sustained response.

18          DR. LIPSKY: Because the inverse was that  
19 those patients who appeared -- the patients who had  
20 the response early on had the longest therapy with  
21 negative -- with inability to detect virus.

22          DR. GRETCH: Exactly. Exact logic. If I  
23 was taking care of a patient and they became negative  
24 at five months, I'd say you probably need to be on it  
25 for a year and a half. I mean, that's just sort of

1 common sense, but you need to show that in a study.

2 DR. LIPSKY: I agree.

3 DR. GRETCH: It took that long to get  
4 negative.

5 DR. LIPSKY: And the mechanism of that, we  
6 simply don't know.

7 DR. GRETCH: Well, we believe it's  
8 possible that there's long lived cells in the liver  
9 the virus is in, or other extra hepatic cells that are  
10 shedding the virus via the rate of their natural death  
11 and turnover, that the virus is really being  
12 inhibited, that there's no replication going on; but  
13 there's cells harboring virus in a "encapsidated"  
14 form. It's infectious, but it's within cells, and as  
15 those cells die, they release virus at a slow rate,  
16 and if you do the mathematical modeling, you could be  
17 consistent with that sort of decay of infected cell.

18 It may also be that 95 percent of  
19 production is inhibited, and there's a five percent  
20 level that is more resistant, and it just takes time.  
21 It takes time for penetrance of drug or burnout of  
22 viral reservoirs or something like that.

23 It's the same questions that we don't know  
24 what's going on in HIV either. This is actually a  
25 better disease to model HIV than HIV, though, because

1 we do have the chance of cure, and this is a wonderful  
2 opportunity to learn about eradication and the  
3 kinetics of eradication in a chronic viral infection,  
4 in my opinion.

5 DR. LIPSKY: Thank you.

6 DR. POMERANTZ: Just a comment. The best  
7 disease to model HIV is HIV. You're --

8 DR. GRETCH: To model eradication. Yeah,  
9 sure. We all want to say we can eradicate HIV.

10 CHAIRMAN HAMMER: Can I -- I'm sorry to  
11 interrupt, but I don't want to get off into a debate  
12 within the committee at this stage, because the  
13 committee will have its chance to internally talk. In  
14 this public arena, I think this is the period to  
15 really direct questions to the sponsor or any other  
16 questions to the agency.

17 Dr. Bertino.

18 DR. BERTINO: I actually have a couple of  
19 questions for the sponsor about kinetics and dynamics.

20 In your clinical trials, did patients who  
21 had more toxicities probably because of bigger drug  
22 exposure -- did they do better clinically in terms of  
23 knockdown of viral load or remission?

24 DR. ALBRECHT: I think we honestly have to  
25 say that in a study of this size that we haven't

1 really been able to model that. We did PPK. If Dr.  
2 Glue would like to address that.

3 DR. GLUE: One of the variables we added  
4 into our PPK model was looking at concentration, and  
5 there really wasn't any clear relationship between  
6 exposure to ribavirin and eventual outcome.

7 We couldn't add interferon concentrations  
8 into that, because with a drug that's cleared as  
9 rapidly as interferon, it wasn't possible to get PPK  
10 samples, but at the moment the issue between exposure  
11 and treatment response is still an open question.

12 When we have the naive database, we may be  
13 able to shed some more light on that.

14 DR. BERTINO: These patients weren't  
15 controlled for food in this -- in your trial. Right?

16 DR. GLUE: Right.

17 DR. BERTINO: Could they take it with or  
18 without food?

19 DR. GLUE: Correct.

20 DR. BERTINO: And I think in the  
21 information that you provided to us, you showed that  
22 with a high fat breakfast, the AUC with ribavirin  
23 increased 70 percent?

24 DR. GLUE: Correct.

25 DR. BERTINO: So are you concerned that,

1 once we get this -- if it gets out into the community  
2 and patients take it twice a day, morning and evening,  
3 you know, with a high fat meal, that you're going to  
4 see a lot more toxicity associated with this?

5 DR. GLUE: Could I have slide 231, please.

6 To go to the data that you're referring  
7 to, these are the mean concentration -- the mean  
8 derived pharmacokinetic parameters in healthy  
9 volunteers who received a single 600mg dose of  
10 ribavirin after receiving a standard high fat meal --  
11 It's the equivalent of a McDonald's breakfast -- or  
12 who received it after fasting.

13 This was a two-way crossover study. There  
14 was a approximately 70 percent increase in Cmax.  
15 There was a 70 percent increase in AUC for fed  
16 relative to fasted, and the Tmax, the time of maximum  
17 concentration, was increased -- was approximately  
18 doubled.

19 Now what implications are there for  
20 bioavailability under multiple dose conditions? It's  
21 very difficult to predict that, firstly because we  
22 know from multiple dose studies that we've done that  
23 you can't predict multiple dose kinetics from single  
24 dose kinetics.

25 An example is the fact that, because

1 there's extensive accumulation, half-life increases  
2 under multiple dose conditions, and one can't use  
3 single dose data to predict what's happened under  
4 multiple dose.

5 Now because of that, we can't use those  
6 data to predict what's going to happen to people who  
7 always take their drug with food compared to those who  
8 don't take their drug with food.

9 Is this likely to be an issue? My opinion  
10 is it's unlikely to be a major issue in that we've got  
11 a factor here that under single dose conditions causes  
12 a 70 percent difference.

13 Now in the pharmacokinetic variability  
14 that we've seen in two multiple dose PK studies that  
15 we've carried out, plus in the population PK, the  
16 multiple dose variability associated with ribavirin is  
17 in the ballpark of 30 percent, and this is much lower  
18 than one would expect to see than if we had a  
19 heterogeneous group of patients, some of whom always  
20 took it fasted, some of whom always took it fed.

21 DR. BERTINO: Okay. I'm not sure I agree  
22 with your statement that -- and actually, you've got  
23 it in the written material the company provided --  
24 that there is a food effect, but in terms of clinical  
25 practices, this is not a critical issue; because if

1 you have patients who take it with food and -- I might  
2 argue with you about single dose and multiple dose  
3 pharmacokinetics and not being able to predict, but if  
4 you have a significant increase -- I mean, if you even  
5 used two one-sided test procedure, this is  
6 significant.

7 DR. GLUE: Oh, it's a significant result.  
8 Yes.

9 DR. BERTINO: That, you know, that you've  
10 got a much bigger drug exposure. So any patient who  
11 drops their dose, whose dose is dropped and maybe, you  
12 know, they've got a lot of, you know, whatever, not  
13 feeling well, not eating well, so their dose is  
14 dropped. Now they're not taking it with food.

15 So you've got this huge variability going  
16 on, and then the question is what happens to your  
17 response rate? I mean, I understand you guys were  
18 trying to look at real world conditions.

19 DR. GLUE: Right.

20 DR. BERTINO: But I think it would have  
21 been useful to have looked and said, well, you know,  
22 you could take it with breakfast and dinner or you  
23 don't. You take it two hours after, you know, or two  
24 hours before or something like that.

25 I actually have a lot of concern about

1 potential for not just toxicity but failure of therapy  
2 because you're bouncing around so much with and  
3 without food.

4 DR. GLUE: You know, I guess the other  
5 approach to take, though, is you've seen the safety  
6 database from the studies, and that is a reflection of  
7 ribavirin use under real world conditions, and one can  
8 manage the toxicities by dose reduction.

9 In practice, one winds up with the  
10 clinical efficacy data and the safety data that we've  
11 achieved. I realize that that skirts around the point  
12 that you're trying to make, but one can manage the  
13 toxicity with dose reduction.

14 DR. BERTINO: Well, but you had a very  
15 toxic -- This is a fairly toxic regimen. I mean, 60-  
16 70 percent of people get some sort of toxicity and,  
17 you know, you've got patients going to their pharmacy,  
18 and the pharmacist -- You know, they're going to ask  
19 the pharmacist, should I take this with food, should  
20 I not take it with food or whatever.

21 So I think that there's -- I still have  
22 these concerns.

23 CHAIRMAN HAMMER: Dr. Jolson, did you have  
24 a comment?

25 DR. JOLSON: Yes, I had a question,

1 because I think that's a very good point that you've  
2 raised. Do you have any suggestions for us for how to  
3 deal with this in the labeling or what recommendation  
4 should be made to patients, given the data that you've  
5 seen?

6 DR. BERTINO: Well, I think, Dr. Jolson,  
7 you know, that I'm not sure that I could come up with  
8 any recommendations, because this study was not food  
9 controlled. So we don't know how patients took it.

10 You know, I guess --

11 DR. JOLSON: But given we have what we  
12 have, what are your thoughts?

13 DR. BERTINO: I just don't think I can  
14 give you a recommendation with or without food. I  
15 think that patients should be consistent probably. If  
16 they're going to take it with food, then they should  
17 always take it with food or they should always take it  
18 on an empty stomach. I think that would be the only  
19 potential recommendation. Maybe Jim Lipsky's got some  
20 idea.

21 DR. ALBRECHT: I think one thing that we  
22 would like to add to this is that we did look at  
23 patients that had dose reduction to determine whether  
24 they broke through, if you will, in the virologic  
25 response.

1                   What we found in most of the Intron  
2 A/Ribavirin patients is they did continue to have a  
3 consistent response. So I think that, you know,  
4 perhaps the accumulation that we're seeing there with  
5 this drug, that, you know, whether they take food one  
6 day and food not the next day, it probably levels out  
7 somewhat, as Dr. Glue was saying.

8                   This is a unique drug in its profile and  
9 the fact that it does accumulate. It's not like it's  
10 here in the morning, and it's gone in the afternoon.  
11 So we do have a level that stabilizes across time.

12                   We did find that, when we had to dose  
13 reduce, those patients actually didn't lose their  
14 response, if they were responding. Now there were  
15 very few patients in this particular study that we did  
16 that. We'll see in the larger study if indeed this  
17 continues to hold true.

18                   DR. LIPSKY: I think the issues, Joe, that  
19 you're bringing up and the FDA's questions are very  
20 pertinent. I think if you go through at least the  
21 data that were presented to us, there are a lot of  
22 holes and a lot of things that need to be looked at,  
23 and maybe the FDA has more.

24                   There are some curious things about the  
25 statements that were made in the package. One is that

1 you have a linear association with increasing the dose  
2 and area under the curve, but yet you have a plateau  
3 effect of the Cmax, and that seems a bit unusual.

4           There was also a statement, and perhaps  
5 it's just simply a misstatement, that quote "the  
6 increased bioavailability of ribavirin in patients  
7 with renal dysfunction appears to be due to changes in  
8 several pharmacokinetic indices, reduced renal  
9 clearance, reduced volume and distribution, and  
10 possibly a slight increase in oral bioavailability."

11           I'm not -- and perhaps that was a  
12 misstatement or I'm not sure what you were meaning in  
13 that.

14           DR. GLUE: Let me try and explain some of  
15 these.

16           DR. LIPSKY: And I do realize that you  
17 were doing the study at maximum tolerated doses, just  
18 to get it on. So I realize that there was certain  
19 driving forces here.

20           DR. GLUE: Let me go through your  
21 questions. Slide 203, please.

22           DR. LIPSKY: And in the background of  
23 this, we don't know whether we want AUC, we want Cmax,  
24 do we?

25           DR. GLUE: I believe that AUC is the

1 critical variable.

2 This is a stylized view of how ribavirin  
3 gets into the body, where it's compartmentalized  
4 within the body, and there were two types of  
5 nucleoside transporters that are involved in getting  
6 it around.

7 There's a concentrated type, sodium  
8 dependent transport of the N1 transporter that's  
9 involved in getting ribavirin from the gut into  
10 enterocytes, and it's also probably involved in some  
11 of the renal elimination of parent ribavirin.

12 The major transporter for ribavirin, once  
13 it's in the body, is an equilibrative type of  
14 transporter, the es transporter, which is a highly  
15 conserved transporter. It's basically on all cell  
16 types, and that's involved in getting ribavirin into  
17 the body and getting it into different cell types.

18 Now the reason that AUC is linear with  
19 dose is that the bioavailability of drug, getting  
20 ribavirin from the gut into the body, is achieved even  
21 though the N1 receptor transporter is saturated  
22 probably after oral doses of 400mg. But the fact that  
23 there is saturation of the N1 receptor beyond the  
24 400mg dose -- the  $K_m$  is in the low micromolar range --  
25 is a reason for the asymptoting of the  $C_{max}$ .

**S A G CORP.**

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1 Now to address your question on renal --

2 DR. LIPSKY: And the AUC -- why does the  
3 AUC go up linearly?

4 DR. GLUE: Because these transporters are  
5 along the entire length of the small intestine. The  
6 major concentration of them is in the jejunum. Even  
7 though one can saturate the transporter, it's still  
8 possible to get essentially the whole dose of drug  
9 absorbed over a one to one and a half hour period,  
10 even though the transporter is temporarily saturated.

11 So the effect is principally on the Cmax  
12 and not on the total bioavailability of the drug.

13 Your next question was on?

14 DR. LIPSKY: That you were relating  
15 changes in bioavailability to parameters of renal  
16 clearance. I'm not -- Unless you're talking about  
17 some first pass effect, I'm not familiar with changes  
18 in bioavailability being related to clearance.

19 DR. GLUE: These were mystifying results  
20 to us as well. Let me go to slide 214, please.

21 The initial hypothesis that we had when we  
22 started the study -- Very little parent ribavirin is  
23 eliminated renally, probably ten percent or so of the  
24 dose. What we found when we did a study in patients  
25 with renal dysfunction -- these are people with normal

1 creatinine clearance. These are people with mild,  
2 moderate and severe reductions in renal function. So  
3 we have creatinine clearances around 60 mls per  
4 minute, around 40 mls per minute, and about 15 mls  
5 per minute.

6 One can see that the mean Cmax -- these  
7 graphs show the individual values plus the mean and  
8 standard deviation. One sees a general increase in  
9 Cmax and a general increase in AUC.

10 Because of the unexpected nature of these  
11 findings, we were able to go back and get about two-  
12 thirds of the patients to participate in IV study. So  
13 we could -- this was after oral 600mg dose. We then  
14 gave patients an IV dose of ribavirin. Next slide,  
15 please.

16 We found the following observations. If  
17 we correlated creatinine clearance in mls per minute  
18 against volume of distribution, what we found is that  
19 as creatinine clearance diminished, so did volume of  
20 distribution, which is -- Obviously, if the drug is  
21 moving least well into other cell types out of the  
22 plasma, this would be one very good reason for the  
23 higher concentrations that we're seeing in these  
24 patients.

25 The second finding, which is most unusual

1 because I don't know of any other examples of it, is  
2 the fact that there's a negative relationship between  
3 creatinine clearance and the absolute bioavailability.  
4 So that we have in people with normal renal function,  
5 absolute bioavailability in the ballpark of 50  
6 percent. As creatinine clearance diminishes, we are  
7 seeing the absolute bioavailability increase up to  
8 perhaps 75 percent.

9 The third thing that we saw, which is not  
10 surprising, is that renal clearance, the ratio of the  
11 amount excreted relative to dose, is also diminished.

12 Why -- The actual mechanisms to account  
13 for the reduced volume of distribution and the  
14 increased bioavailability as renal function goes down  
15 is -- I can't explain, but these would explain why the  
16 exposure is greater in these patients.

17 CHAIRMAN HAMMER: Thank you. Can we have  
18 the lights, please.

19 I'd like to ask the sponsor a sort of  
20 three-part question. We've heard bits and pieces of  
21 the current and future clinical development plan. I  
22 think it would be helpful to the committee to know  
23 what trials -- just a brief summary of what trials are  
24 in place, what trials are planned.

25 A second question would be what practical

1 recommendations for monitoring would the sponsor make.

2           The third is what is the commitment to  
3 population based or epidemiological studies to get at  
4 some of the issues of long term outcome, cirrhosis,  
5 cancer, death, as well as some of the safety issues  
6 that have been brought up?

7           I'd be happy to reiterate those, but let's  
8 start perhaps with the clinical development plan as it  
9 stands and what's planned.

10           DR. ALBRECHT: May I have slide 8, please.

11           This is the slide that I showed at the  
12 beginning of the presentation, and we'll just walk  
13 through it to show you what's currently ongoing.

14           The focus of the discussion today has been  
15 the relapsed patients in the two trials. We also have  
16 ongoing a Phase III in naive patients. Those are also  
17 two independent trials, one conducted in the United  
18 States, the other one conducted in Europe, Canada,  
19 Israel and Australia.

20           These trials each have between 800 and 900  
21 patients in them. The data as we show it here shows  
22 the data pool. There's a pool of 1744 patients.  
23 These trials were designed to look at the question, I  
24 think, that we've been alluding to, and that is  
25 whether duration of therapy makes a difference.

1           One of the questions that you asked us is,  
2 if those patients that first became negative after  
3 week 12 had been treated longer, would it have perhaps  
4 resulted in higher response rates?

5           What we know from alfa interferon  
6 monotherapy in trials that we conducted with Intron A  
7 is that you can reduce relapse by extending the  
8 therapy. So this study is basically completed  
9 clinically, and we will be developing the data very  
10 shortly.

11           So this trial is designed to look at the  
12 naive patients, a much broader patient population, and  
13 also to evaluate duration of therapy, 24, 48 weeks.

14           The other study that I discussed this  
15 morning was one, I think, that is very relevant to  
16 your questions about toxicity. That is that we are  
17 looking at the optimum dose of Rebetol. I'll describe  
18 this study just briefly, although we didn't bring a  
19 diagram of it.

20           The study is actually a two-stage study.  
21 In the first stage of the study we looked at 400, 600,  
22 800 and 1,000-1200mg of ribavirin administered with 3  
23 million units TIW, compared to an Intron A/placebo  
24 control, as we've used in all our studies.

25           We did a stage 1 analysis to show us what

1 the response was with regard to hemolysis. Hemoglobin  
2 was a primary criteria, and the other thing that we  
3 looked at was reduction in virus at 12 weeks.

4 We then selected a dose, based on this  
5 interim analysis, and we're adding additional patients  
6 to the doses that are being evaluated. The dose  
7 selected from the 4-6-800 group compared to the  
8 control, which is the 1,000-1200mg, compared to the  
9 Intron A/placebo control.

10 That trial is ongoing at the present time.  
11 We will end up with basically 175 patients in each of  
12 the treatment groups. So we will have the dose  
13 response to tell us whether a lower dose of ribavirin  
14 administered with a 3 million units TIW Intron dose is  
15 equally effective to 1,000-1200mg ribavirin.

16 That study is ongoing at the present time,  
17 and will be finished sometime early in the next year.

18 We do have a study that isn't listed on  
19 here that, I think, will be very interesting, and it's  
20 currently under development. So it is not -- does not  
21 have a protocol design, but Dr. Gretch mentioned the  
22 concept of perhaps bringing the virus load down  
23 faster, i.e., daily dosing, higher doses, that kind of  
24 study design.

25 We have on the drawing board discussions

1 as to whether we should begin to look at things like  
2 daily dosing or higher doses in combination with  
3 ribavirin in an effort to bring the virus load down  
4 faster and perhaps increase the response rate.

5 I did mention to you previously, we do  
6 have studies going on in transplant patients. We are  
7 cooperating with Amfar to do a study in the coinfecting  
8 HIV patient. I think, in fact, they've just had their  
9 investigators meeting to initiate the trial.

10 We have studies that are ongoing in  
11 nonresponder patients to interferon. Those are  
12 patients that didn't previously respond to interferon,  
13 and are now being treated with a combination.

14 So we have a fair number of studies going  
15 on in compensated hepatitis, as well as our study that  
16 we're doing in transplant patients.

17 CHAIRMAN HAMMER: Well, parts 2 and 3 were  
18 what your recommendations would be if this combination  
19 product is out there for monitoring, particularly  
20 since there is no approved quantitative HCV RNA test,  
21 and also the population based sorts of studies that  
22 everyone might be interested in for long term follow-  
23 up and what the sponsor's thoughts are about that and  
24 cooperating with the agency on finding out what  
25 happens over the next ten to 15 years.

1 DR. ALBRECHT: Let me first address the  
2 issue about monitoring. I think there's kind of two  
3 parts to that, one part being the safety. I think  
4 that we've said very clearly that we see -- when we  
5 see hemoglobin decrease, it really decreases quite  
6 rapidly, usually within the first two weeks.

7 So we actually have proposed a monitoring  
8 schedule that includes evaluation of patients at two  
9 weeks after the start of therapy, because this is  
10 really when you begin to get the feeling of how -- or  
11 you begin to see how much the hemoglobin has dropped  
12 and what you need to do.

13 So what we recommend is that the patient  
14 be seen at two weeks, and then a physician has to use  
15 his own judgment. Does the patient need to be seen  
16 again at three weeks or is it okay to bring them back  
17 at four weeks.

18 As we've shown you, the nadir with most of  
19 these patients occur by four weeks. So you can then  
20 perhaps go on a bit less rigorous schedule, maybe  
21 every two weeks or at the end of a month. We can,  
22 from our clinical trials, show that this does indeed  
23 provide safe monitoring. You need to dose reduce,  
24 obviously, when you see that that hemoglobin is  
25 dropping.

1           With regard to the monitoring for  
2 virology, I think that you need to start out knowing  
3 the patient is HCV RNA positive. Most antibody  
4 patients, antibody positive patients, are HCV RNA  
5 positive. So I think there's very little danger that  
6 you're going to treat a patient that isn't anti-HCV  
7 positive, if you use an antibody test.

8           If you really want to look at whether the  
9 patient is responding virologically, you're going to  
10 need to use a test that is an experimental test, that  
11 is not licensed, but is available. You don't need a  
12 quantitative test like we've used. A qualitative test  
13 is fine, and you can take a look and see whether the  
14 patient is virologic negative.

15           We did show you in this data that  
16 virtually everybody who receives the combination and  
17 is ALT normal is also virus negative. This is very  
18 interesting. It's in contrast to what you see with  
19 Intron or the other alfa interferons monotherapy, in  
20 that you'll have a proportion of patients who remain  
21 ALT negative but not virus negative.

22           I think that one of the problems that we  
23 do have in recommending HCV RNA testing is that there  
24 is not a licensed test.

25           CHAIRMAN HAMMER: We've seen that problem

1 in other diseases.

2 DR. ALBRECHT: I hope we're moving towards  
3 in the future something so that -- This testing is  
4 available, but it is not licensed for diagnosis or for  
5 evaluation of therapy; but you've seen that before.

6 CHAIRMAN HAMMER: Yes. Again, the issue  
7 of you've got a huge safety data base, and what are  
8 your current long term follow-up plans that you have  
9 in place for all patients who have been treated, and  
10 what is the commitment, in part safety, of course,  
11 because of some of the issues that have come up, but  
12 also long term outcome which would be really critical  
13 to try to accrue, as far as cirrhosis, cancer,  
14 transplantation, death outcomes which, obviously, at  
15 clinical trials will provide some database for that  
16 with long term follow-up, but a broader population  
17 based sort of study might be helpful to us, given the  
18 worldwide epidemic.

19 DR. ALBRECHT: I think at the end of the  
20 day in -- let's start with clinical trials, and I  
21 mentioned this previously. We have on trial now in  
22 our SPR -- Schering-Plough Research Institute trials  
23 about 2500 patients, not all of them treated with the  
24 combination.

25 We do offer -- At the end of the clinical

1 trial, we ask the patient -- we certainly can't force  
2 them to do it -- to enter into a five-year follow-up.  
3 So we will have follow-up on our patients in the trial  
4 that were treated, and I think that's very important.

5 The patients are to be seen six months  
6 after the end of the study, which is actually one year  
7 after treatment, and then they're to be seen once a  
8 year thereafter. They will have virologic testing, a  
9 biochemical testing, and assessment of their liver  
10 disease.

11 As I indicated previously, I think we'll  
12 hang onto most of the patients that are PCR negative.  
13 They want to be followed up. It doesn't cost them  
14 anything, and we will find out whether indeed their  
15 disease progresses.

16 I think we're going to have a much harder  
17 time following those patients that remain PCR  
18 positive, because in reality there are going to be new  
19 therapies. At least, I hope there are going to be new  
20 therapies. We are certainly working on it, and those  
21 patients will end up in other trials. So we may lose  
22 them.

23 I think at this time we actually do not  
24 have formulated plans with regard to any kind of a  
25 population follow-up on these patients.

1 CHAIRMAN HAMMER: Thank you. Are there  
2 any last questions before we come to the questions.  
3 Roger?

4 DR. POMERANTZ: Yes, a real quick  
5 corollary. Does anyone from the FDA or the committee  
6 know how close a HCV PCR is to FDA licenseship? I  
7 mean, there's close and there's close, as we've  
8 learned from other fields, because it is going to be  
9 important for this, especially as it starts getting  
10 into the patients and used in different groups. Do we  
11 have any idea about that?

12 DR. MURPHY: Even if we do, we couldn't  
13 tell you.

14 DR. POMERANTZ: Okay. Fine.

15 DR. JOLSON: But we're aware that it's a  
16 problem.

17 CHAIRMAN HAMMER: Thank you.

18 DR. GRETCH: Ongoing trial? We can't make  
19 you aware of ongoing Phase III trials of a qualitative  
20 test? That's something we can't be aware of?

21 DR. JOLSON: If you're aware of  
22 information, the committee members are free to discuss  
23 it. We're not in a position where we can discuss it.

24 DR. GRETCH: There's a qualitative assay  
25 that's in Phase III trial that has 100 copy

1 sensitivity that I think will probably do well and  
2 receive licensure. That's my, you know, prediction,  
3 my crystal ball.

4 CHAIRMAN HAMMER: Dr. Self.

5 DR. SELF: Just a clarification. In the  
6 long term follow-up of patients in the clinical  
7 trials, you said that it would be difficult to follow  
8 those who are PCR positive. You'll attempt to follow  
9 them, but you expect a lower success rate, or you will  
10 plan not to follow that subset?

11 DR. ALBRECHT: We will attempt to follow  
12 those patients. However, as I said, I expect those  
13 patients, even though they enroll in the follow-up,  
14 will drop out when a new therapy comes along, because  
15 what will happen to them is, if there is a new therapy  
16 available, they obviously will accept it, and they'll  
17 drop out of our follow-up.

18 The protocol is written to follow all  
19 patients. However, if they do go on another therapy,  
20 they then drop out of this study, because we think the  
21 data is no longer relevant.

22 CHAIRMAN HAMMER: But I would just say  
23 long term follow-up, irrespective of what treatment a  
24 patient goes on subsequently, is -- that's still quite  
25 valuable information. Dr. Hamilton.

1 DR. HAMILTON: I have a question for Dr.  
2 Albrecht. I may have missed this in her opening  
3 remarks, but I didn't hear a characterization of what  
4 the baseline clinical status was of those patients  
5 entered. That is, were they symptomatic and, if so,  
6 to what extent; and in that regard, if they were  
7 largely asymptomatic, which I believe in my experience  
8 many are, what we would be asking them to do in  
9 embarking on a six month course of combination  
10 therapy, let's say, is to expect the toxicities that  
11 you identified.

12 Therefore, the questions are two: One,  
13 are there some clinical data at baseline; and  
14 secondly, have you given any consideration to doing  
15 quality of life kinds of estimates?

16 DR. ALBRECHT: Yes, we did do quality of  
17 life estimates in these patients, and we do have the  
18 data, if you'd like to see it. We did look at --

19 DR. HAMILTON: A brief summary.

20 DR. ALBRECHT: Basically, I think -- and  
21 Dr. Davis maybe can -- Okay. Dr. Davis has earlier  
22 taken a look at baseline characteristics using quality  
23 of life estimates, SF-36 which we used in this trial,  
24 which does show that the chronic hepatitis C patient  
25 does not meet the norms for other populations.

1           So while they may not be symptomatic in  
2           the sense that they express themselves  
3           symptomatically, when you look at their quality of  
4           life, they do have a diminished quality of life.

5           We did look at the SF36 in this study with  
6           a validated module for hepatitis C. What we found is  
7           that, yes, as we expected, that these patients do have  
8           a diminished quality of life. They're particularly  
9           diminished in areas of vitality and social interaction  
10          and so forth.

11          One tends to look at this data and think  
12          these patients may look like people who are continuing  
13          to do their daily job, but yet are suffering in social  
14          areas, probably because of the fatigue that's  
15          associated with the disease. So, yes, we did look at  
16          the quality of life data to see what they looked like  
17          at baseline.

18          DR. HAMILTON: Well, if you have that in  
19          hand, then perhaps a short term relook at those  
20          patients who have succeeded and/or not succeeded in  
21          neutralizing their virus would be useful.

22          DR. ALBRECHT: May I have slide 93,  
23          please. Is that the correct one?

24          DR. HAMILTON: Yes. Both follow-up data  
25          and differences between groups.

1 DR. ALBRECHT: This is probably the data  
2 that -- It's quite difficult to explain, but I will  
3 attempt to do so. I know it's very small.

4 This is health related quality of life.  
5 What we looked at is -- this is basically  
6 responder/nonresponder data, looking at their quality  
7 of life six months following the end of therapy.

8 What we found is in patients that are  
9 overall responders -- Now these are the patients that  
10 we classified as both histologic and virologic  
11 responders. -- that we did see an improvement in those  
12 patients relative to the SF36.

13 What you're seeing here are the blue  
14 scores. Plus is better. These are the overall  
15 responders. The yellow, as opposed to what I  
16 previously showed you is not the Intron/placebo  
17 control. These are only the Intron/ribavirin  
18 patients. They do not have as good a score.

19 Some of the changes were statistically  
20 significant, if you look at them in a subpopulation;  
21 but this is not an over -- this is not an all-treated  
22 patient analysis.

23 So, yes, we do see some change in the  
24 overall responders in that they are better by the  
25 quality of life measurements when they are overall

1 responders.

2 CHAIRMAN HAMMER: Thank you. Can we have  
3 the lights, please.

4 DR. SELF: Is there a difference between  
5 the two treatment groups in the quality of life  
6 measurements?

7 CHAIRMAN HAMMER: Okay.

8 DR. ALBRECHT: I think that the other  
9 question you had was with regard to the patient status  
10 at baseline relative to their liver disease. These  
11 were compensated patients. Therefore, they had normal  
12 albumins, normal bilirubins, normal prothrombins, no  
13 history or presence of ascites or bleeding varices.  
14 They basically have had no signs of liver  
15 decompensation.

16 So, clinically, they were well, and  
17 actually biochemically they were well, with the  
18 exception of the elevated ALTs and the liver histology  
19 inflammation.

20 CHAIRMAN HAMMER: Thank you. One last  
21 question.

22 DR. SELF: I'm not sure I fully understand  
23 the quality of life data. That was -- The comparison  
24 that I was interested in is quality of life measures  
25 during the follow-up period compared between the two

1 groups. Is that correct? Then there's no difference  
2 between -- was not different? Thank you.

3 CHAIRMAN HAMMER: Thank you.

4 DR. ALBRECHT: One of the reasons that we  
5 think that we may not have seen any difference is the  
6 sample size. Now in the studies that you asked me to  
7 describe, those studies also have quality of life data  
8 being analyzed. So probably when we get to 1800  
9 patients, we'll be able to more definitively tell if  
10 we have a difference.

11 CHAIRMAN HAMMER: Thank you. This is the  
12 last question before we move on.

13 DR. LIPSKY: And for the FDA, if the FDA  
14 were to approve this drug combination for this  
15 indication, which I think would be retreatment with  
16 patients who failed interferon, would there be any  
17 ethical problems in maintaining naive patients? Would  
18 they be so different, you know, who would possibly be  
19 on placebo, particularly when we've talked about cure?

20 I mean, some people have talked about cure  
21 today.

22 CHAIRMAN HAMMER: That's for us to  
23 discuss, I think.

24 DR. BEHRMAN: What would you like?

25 CHAIRMAN HAMMER: First, well, I think the

1 question was posed to you. So, please, if you want to  
2 field it.

3 DR. BEHRMAN: There are a couple of ways  
4 to answer that. One is that the question is probably  
5 -- We believe it's an open one as to whether the  
6 populations will respond essentially similarly. If we  
7 believe the populations were that similar, we could  
8 then grant a broader indication, but we would agree  
9 with what you said, that the indication before us  
10 today is relapsed patients.

11 So we would not have an ethical problem  
12 with the trials continuing. The other sort of broader  
13 question which, in a sense, we're asking you to  
14 address today is -- and it gets back, I think, to what  
15 Dr. Hamilton was alluding to and we've spoken a little  
16 bit about before -- we don't fully understand or we're  
17 hoping you'll help us understand, if you can, what --  
18 We understand what the data speaks to the six months  
19 and to the six months of follow-up, but what that  
20 means down -- in the long term is somewhat unclear.

21 So, therefore, that again enters into the  
22 issue of what kind of trials are ethical or not  
23 ethical.

24 CHAIRMAN HAMMER: Thank you. With that,  
25 we'll begin the formal charge to the committee, which

1 is to put forward in a series of questions, and the  
2 committee will deal with the first question initially,  
3 because the others follow with what our response is.

4 I'll read that question for the group and  
5 for the record: Is ribavirin in combination with  
6 interferon alfa-2b recombinant safe and effective for  
7 the treatment of hepatitis C virus? If no, what  
8 additional study is warranted? If yes, we go on to  
9 other questions.

10 I think we will start and give each member  
11 of the committee a chance to speak. So I'll start on  
12 my right this time with Dr. Lipsky.

13 DR. LIPSKY: Thank you. Well, we have  
14 seen evidence from two pivotal studies done in  
15 different geographic locations which give virtually  
16 identical results, which show after a limited period  
17 of follow-up very promising results, with the  
18 possibility of permanent viral eradication. That is  
19 based on one of the members of the panel who believes  
20 that the hepatitis C disappeared for a long enough  
21 time, I guess, it should -- if it doesn't bounce back,  
22 it should have bounced back.

23 In view of the outcome of the disease, is  
24 it safe? Well, obviously, it's not, you know,  
25 completely safe, but no medicine is completely safe,

1 but there the risk benefit would certainly be in the  
2 favor that a certain subset of these patients respond  
3 well, at least as measured in the duration of the  
4 study.

5 So the answer is yes.

6 CHAIRMAN HAMMER: Thank you. Again, the  
7 subsequent questions we'll deal with later as a group.  
8 Dr. Pomerantz?

9 DR. POMERANTZ: The answer is yes. I gave  
10 a little bit of a hard time to Dr. Gretch before, but  
11 I think it's important to point out that he was very  
12 right. This, in my mind, is a viral disease.

13 As is for many chronic viral infections,  
14 you're not going to know what's going to happen over  
15 six months, but you can make some educated guesses  
16 that getting the virus to undetectable levels is  
17 important, both for the immune system as well as for  
18 direct viral effects in the liver.

19 I think that this is shown about as  
20 clearly as I've seen for hepatitis C, and even though  
21 60 to 70 percent having adverse effects is nothing to  
22 sneeze at, it is clearly in 1998 a useful adjunct.

23 CHAIRMAN HAMMER: Thank you. Dr. El-Sadr.

24 DR. EL-SADR: It's interesting that the  
25 question is, is it effective treatment of hepatitis C

1 virus, although we haven't shown that it's an  
2 antiviral, but that's another story.

3 I am encouraged by the effect that's been  
4 shown with the combination on the liver biopsy. I  
5 think there are at least some data that I'm aware of  
6 that the changes in liver histology are probably the  
7 ones that suggest the -- that are associated or  
8 correlated with ultimate outcome of the patient.

9 I think the PCR effect of the combination  
10 indicate that this has an effect on the -- an  
11 antiviral effect of some kind, but whether this will  
12 mean it is a durable clinical benefit, we're not sure  
13 yet.

14 So I do agree with the statement. I think  
15 it's specifically as was demonstrated in this study,  
16 which was in mild disease in patients who had rather  
17 a long list of restrictive eligibility and exclusion  
18 characteristics.

19 CHAIRMAN HAMMER: Thank you. Dr.  
20 Hamilton.

21 DR. HAMILTON: My answer is a qualified  
22 yes, within the limits of the study as presented here  
23 with a select patient population with a specified  
24 duration of applicability and eligibility for this  
25 trial.

1 I think further data should be forthcoming  
2 at some level to independently confirm the merits of  
3 the surrogate markers employed very heavily here, and  
4 I actually have a suggestion there that the company  
5 may want to entertain, which includes acquisition of  
6 a clinical dataset that's accompanied by plasma  
7 specimens that have been in the freezer for years and  
8 years.

9 There have been a lot of such studies  
10 around. I find it hard to believe that there wasn't  
11 someone who wanted to collaborate with you that would  
12 provide long term clinical information with sets of  
13 plasma serum that could be accessed to your mutual and  
14 our definite benefit.

15 I'd like to see some further information  
16 on the pathogenetic factors that are going on here.  
17 I'd like some reassurance that, in fact, what's going  
18 on in the plasma is going on in the liver.

19 With those caveats, however, I would say  
20 that this combination should be seriously considered  
21 by practitioners in this field in these 1990s.

22 CHAIRMAN HAMMER: Thank you. Dr.  
23 Feinberg.

24 DR. FEINBERG: I do also agree that the  
25 combination has been shown to be safe and effective in

1 these studies. I really don't have a whole lot to say  
2 that hasn't already been said by the speakers before  
3 me. It is, however, exciting to see progress made in  
4 another viral disease besides HIV.

5 CHAIRMAN HAMMER: Dr. Self.

6 DR. SELF: Well, I'm going to squirm a  
7 little bit. I'm not sure if the wording of this  
8 question was -- how clever that was. They're always  
9 clever, these questions.

10 CHAIRMAN HAMMER: Yes.

11 DR. SELF: Is it effective for the  
12 treatment of hepatitis C virus? Yes, clearly. Viral  
13 load went down. Is it effective for treatment of  
14 patients infected with HCV? I've heard no data  
15 presented today to be able to use to address that  
16 question, though one possibility in the short term was  
17 the quality of life data where there is no difference  
18 there, and we simply don't know in the long term what  
19 this will translate into clinically.

20 CHAIRMAN HAMMER: Thank you. Dr. Bertino.

21 DR. BERTINO: I feel like I'm at a joint  
22 commission meeting here. It depends on the  
23 definition--

24 CHAIRMAN HAMMER: I'm not sure how to take  
25 that.

1 DR. BERTINO: Well, about safe. I think,  
2 yes, it's effective. Safe -- you know, 60 percent  
3 toxicity rate is pretty high, and I don't know what  
4 other drugs that we use that have a 60 percent  
5 toxicity rate. I'm sure there are a number of them,  
6 but I think, relatively speaking, because the  
7 mortality rate was very low in the studies presented,  
8 I would vote yes.

9 CHAIRMAN HAMMER: Thank you. Ms.  
10 Pollichino.

11 MS. POLLICHINO: Speaking as a patient,  
12 I'm very encouraged by the results of the study as to  
13 the efficacy. I do have some concerns about the  
14 toxicity, and maybe some of that can be addressed in  
15 the labeling. I'm not quite sure, but the answer is  
16 yes.

17 CHAIRMAN HAMMER: Thank you. Dr.  
18 Zimmerman.

19 DR. ZIMMERMAN: It's hard not to sound as  
20 though you're echoing somebody, but I think the  
21 evidence is very compelling that something new is  
22 being done to hepatitis C. Indeed, something new is  
23 being done to viral disease in this phenomenon that I  
24 think is very important.

25 From all the evidence we have now,

1 clearly, it would warrant support and use. I would  
2 like to conceive of some means of distinguishing  
3 responders from nonresponders, and further studies  
4 after the drug was in use ought to be directed at that  
5 to see if the nonresponders could be converted to  
6 responders.

7 CHAIRMAN HAMMER: Good point. Dr.  
8 Friedman.

9 DR. FRIEDMAN: Again, I hesitate to echo  
10 everything that's been said, but I come from this from  
11 the point of view of a clinician who takes care of  
12 many patients with hepatitis C.

13 I would just add this perspective. In the  
14 real world interferon alone is not a terribly useful  
15 drug. It's fraught with toxicity, and it's relatively  
16 ineffective. It seems to me, on the basis of the data  
17 presented, that the combination of interferon plus  
18 ribavirin will be more effective and will be less  
19 cumbersome to use because of the six month treatment  
20 period.

21 As far as the toxicity is concerned, I  
22 think that's relative also. Much of the toxicity  
23 relates to interferon, which is already an approved  
24 drug, and I think the question is what is the marginal  
25 additional toxicity.

1 I'm not sure we know the -- other than the  
2 hemolysis issue, I don't know if we really know the  
3 answer to that question, but it doesn't seem to be  
4 very great.

5 CHAIRMAN HAMMER: Thank you. Dr. Gretch.

6 DR. GRETCH: I have to be qualified also.  
7 I don't know the way the FDA works in terms of drug  
8 development. I think that the presenters have clearly  
9 shown efficacy and safety, but there's also a  
10 disappointment, because I think that there is clear  
11 data supporting RNA, quantitative RNA, as a valuable  
12 marker for dose optimization studies, preclinical  
13 studies.

14 I think that that's been very successfully  
15 done for modeling HIV and that the hepatitis C field  
16 needs to follow that, especially as new drugs come on  
17 board.

18 So I think that the presenters have their  
19 work cut out in terms of post marketing research. We  
20 still have only a 24 percent response in the major  
21 viral infection, genotype 1 with high viral load, and  
22 that needs to be addressed with more aggressive type  
23 regimens, perhaps induction dosing with interferon  
24 followed by additional ribavirin.

25 It's going to be very important to figure

1 out how to use these drugs safely in combination, and  
2 I think that also a very careful retrospective  
3 analysis of responders and nonresponders in terms of  
4 sequencing of the virus may be important, and I would  
5 also challenge Schering to do those studies in the  
6 post marketing phase, but I think that the drug is --  
7 They've demonstrated what they came to demonstrate.

8 CHAIRMAN HAMMER: Thank you. Just a few  
9 comments from me. First, on behalf of the committee,  
10 I think the sponsor should be commended for performing  
11 these trials, also for putting together a briefing  
12 packet that was lucid and for a presentation this  
13 morning that was also lucid.

14 I think there are a number of caveats in  
15 what we've seen today, which are more a manifestation  
16 of what we don't know in the disease, but that  
17 progress clearly has been made.

18 First, we see a good response rate, but I  
19 think we would all agree that the response rate, even  
20 in the combination, is not optimal. There, obviously,  
21 is a substantial toxicity profile. It's not the most  
22 convenient regimen, since one agent is parenteral.  
23 Another agent has been a mystifying antiviral and has  
24 teratogenicity.

25 With respect to the issue of safety,

1 safety is always relative and, given the serious  
2 nature of hepatitis C disease which does not have to  
3 be restated, an acceptable high toxicity profile, if  
4 properly used by trained clinicians and educated  
5 patients, would work.

6 That being said, there is clear evidence  
7 of efficacy and an advance over existing therapy, and  
8 most importantly, I think it's a basis for future  
9 progress.

10 So I would agree, with the issues of the  
11 disease we're dealing with, that safety is adequately  
12 demonstrated with a number of issues, which we'll  
13 discuss, I think, in the subsequent phase of this  
14 meeting and, clearly, efficacy above where we are has  
15 been demonstrated in two well done studies that  
16 parallel one another.

17 Now it's time to vote. This is the only  
18 question we'll vote on today. The voting members are:  
19 Doctors Feinberg, El-Sadr, Lipsky, Hamilton,  
20 Pomerantz, Self, Bertino, and me.

21 I would restate the question and then we  
22 will have the vote: Is ribavirin in combination with  
23 interferon alfa-2b recombinant safe and effective for  
24 the treatment of hepatitis C virus?

25 All those who think yes on the list of

1 eight members I mentioned, please raise your hand.

2 I believe that was unanimous. Any  
3 opponents? No. Okay.

4 What I think we should do in fairness to  
5 everyone is take a 15 minute break, and then we'll  
6 consider the remaining questions. Thank you.

7 (Whereupon, the foregoing matter went off  
8 the record at 2:24 p.m. and went back on the record at  
9 2:46 p.m.)

10 CHAIRMAN HAMMER: Could I ask people to  
11 please migrate to their seats for the latter part of  
12 the afternoon. If I could call this session to order.

13 In the final session this afternoon, we're  
14 going to deal with three questions which are nonvoting  
15 questions, but are very important follow-ups to  
16 today's discussion and our vote.

17 There are three questions, and what I will  
18 ask, if I can, each of the members of the committee to  
19 deal with in turn is really to take all three  
20 questions as a group and just deal with them one at a  
21 time.

22 The questions are: In which population of  
23 patients is safety and efficacy supported?

24 The following question is: Is there  
25 sufficient information to provide guidance on

1 monitoring of patients during therapy?

2 What issues must be addressed post  
3 marketing?

4 I would just ask each member to comment on  
5 these. Dr. Gretch, could you please start?

6 DR. GRETCH: I've only seen data to  
7 warrant safety and efficacy in the retreatment  
8 patients who have had a biochemical response to  
9 previous therapy. I believe that will probably cover  
10 patients who have had a previous virologic response to  
11 therapy who relapsed after discontinuing therapy. I  
12 would recommend that be the indication.

13 In terms of monitoring, I don't think --  
14 I guess I agree with Jan that PCR testing at three  
15 months is probably a useful recommendation to make if  
16 clinicians can identify a lab that has a good  
17 proficiency, which is one of the problems we have with  
18 HCV RNA testing at the current moment.

19 It's a poor performance of clinical  
20 laboratories during the testing that's been documented  
21 by CAP inspections.

22 I think there's sufficient information for  
23 monitoring of side effects, as presented by the  
24 sponsors.

25 I think the post marketing issues

1 addressed the fact that we have -- most patients in  
2 this country have genotype 1, and many of them have  
3 high viral loads or at least above 2 million, which is  
4 a poor response group or relatively poor, with the  
5 combination 24 percent, and I think that post  
6 marketing studies looking at more aggressive ways to  
7 deal with the viral infection in those select  
8 populations are warranted.

9 I think that we also need to look at  
10 tailoring type regimens in terms of, if we're  
11 monitoring patients and we're not seeing an  
12 appropriate virologic response, are there dose  
13 modification situations that can occur that can be  
14 helpful for individual patients such as going to a  
15 more aggressive dosing regimen or, in fact, as I  
16 mentioned before, starting patients who aren't  
17 responding with -- maybe after a washout period  
18 starting them with an aggressive daily interferon  
19 induction or actually doing studies with twice a day  
20 interferon loading -- patients seem to be tolerating -  
21 - and then adding ribavirin at a specific point in  
22 time in combination, backing off on interferon.

23 I think that these post marketing type  
24 studies are sort of approaching the innovative use of  
25 the drugs in combination with the virologic markers.

1 I would encourage Schering to continue, and I think  
2 that they're doing an excellent job in supporting  
3 investigator initiated studies in these areas.

4 I think that we still need to learn if we  
5 do have the most sensitive assay, the 100 copy  
6 sensitivity assay, for eradication of virus or can we  
7 get ultra ultra sensitive, down to ten copies, or in  
8 fact there's some evidence that monitoring of whole  
9 blood may be more sensitive than monitoring serum or  
10 plasma for hepatitis C.

11 So that I think that some post marketing  
12 studies looking at the monitoring virological assays  
13 might be useful, provide important information to help  
14 clinicians and, obviously, the FDA to make decisions  
15 in the future.

16 I think retrospective studies of the viral  
17 genes in nonresponders and responders tell us an awful  
18 lot about the virological basis of response. We know  
19 that viral load and genotype are clearly predictors of  
20 response or nonresponse in retrospective studies and  
21 also now in prospective studies.

22 I think that it's possible that with  
23 sequencing we can find genes that would predict  
24 response or nonresponse to the combination therapy,  
25 with the hypothesis that ribavirin might be working as

1 an antiviral at a direct spot within the genome of  
2 hepatitis C, perhaps the polymerase gene NS5B.

3 I also believe that I would encourage long  
4 term follow-up studies looking at histology in the  
5 responders and nonresponders. There may be a further  
6 separation of the histologic benefit in the groups.  
7 There may be benefit of therapy, regardless of  
8 virologic outcome, both in terms of histologic  
9 improvement and clinical outcome. So I encourage  
10 those long term follow-up studies, as others have  
11 recommended.

12 CHAIRMAN HAMMER: Thank you. Dr.  
13 Friedman.

14 DR. FRIEDMAN: I agree with much of what  
15 David said. I think that the data provided allow us  
16 only to approve this for relapsers. I would point  
17 out, however, that in the real world I think that many  
18 naive patients, who are very well informed when they  
19 get to the gastroenterologist or hepatologist, are  
20 going to request the combination therapy right off the  
21 bat.

22 Six months of combination therapy as  
23 opposed to 18-24 months of interferon alone is going  
24 to see highly desirable, but we certainly don't have  
25 the data on which to make a recommendation for naive

1 patients.

2 With regard to monitoring, it's standard  
3 practice, I think, among hepatologists to check an HCV  
4 RNA level at three months and use that as the basis of  
5 deciding whether to continue interferon for a longer  
6 period of time. So they've got in the habit of doing  
7 that, and then checking an HCV RNA six months after  
8 completion of therapy.

9 What they're not going to be in the habit  
10 of doing is monitoring the hemoglobin and making dose  
11 adjustments for ribavirin based on changes in  
12 hemoglobin. So I think we really have to focus on  
13 adding those guidelines to our recommendations for  
14 monitoring patients.

15 As far as issues to be addressed post  
16 marketing, again from a practical point of view, dose  
17 response and duration response issue are going to be  
18 very important, as well as side effects. I think it's  
19 going to be particularly important to monitor -- do  
20 long term studies monitoring cardiac and psychiatric  
21 side effects.

22 I think it will be of interest to work out  
23 the mechanism of action of this drug, which doesn't  
24 alone seem to lower HCV RNA levels, and that's going  
25 to be of interest, and then expanding indications,

1 including treating naive patients, pediatric patients,  
2 patients with cirrhosis and more advanced liver  
3 disease.

4 CHAIRMAN HAMMER: Thank you. Dr.  
5 Zimmerman.

6 DR. ZIMMERMAN: It's hard to add to what's  
7 been said again, but I certainly agree with the RNA  
8 monitoring at three months and six months. Nothing  
9 has been said about amino transferase monitoring, and  
10 I think the monthly monitoring to see direction of  
11 response is very pertinent.

12 It goes without saying that the hemoglobin  
13 monitoring -- I do think that along the way subsets of  
14 patients who respond, don't respond, should be  
15 characterized as completely as possible with regard to  
16 whatever genetic characteristics there are, such as  
17 HLA typing and so forth.

18 We keep looking at the virus, but I think  
19 we might look more closely at the host in this  
20 interchange, but needless to say, the population that  
21 it should be approved for is clearly those that are  
22 the relapsers, because that's all we've seen today.

23 CHAIRMAN HAMMER: Thank you. Ms.  
24 Pollichino.

25 MS. POLLICHINO: Yes. I have a concern

1 about the -- If it becomes readily available, I know  
2 many hepatologists are prescribing interferon very  
3 responsibly, but there are also many hepatologists,  
4 GIs and primary care physicians who are not, and I  
5 know that from experience.

6 I just -- I'm very concerned with will the  
7 guidelines very clearly state the monitoring of the  
8 hemoglobin, bold caps. I would recommend, the way  
9 many sometimes -- It's just scanned. You know, the  
10 guidelines are just scanned quickly. Okay, you have  
11 hep C; we're putting you on this regimen.

12 I do have a lot of concerns about critical  
13 drops in hemoglobin.

14 CHAIRMAN HAMMER: Thank you. Dr. Bertino.

15 DR. BERTINO: I believe that the  
16 population of patients that we saw today mainly are  
17 the people that have relapsed after a course of  
18 interferon. In addition, I gleaned -- I think I  
19 gleaned from the protocol that patients with renal  
20 impairment were excluded from the protocol, although  
21 it didn't say specifically in your exclusion slide.

22 So I think, you know, my concern is that  
23 once it gets out there that everybody is going to be  
24 using it on everybody. So, you know, I think that's  
25 a potential big problem.

1 Information on monitoring of patients:  
2 Once again, I think in terms of the efficacy, I would  
3 agree with what has been previously said. I think we  
4 need to make people very aware of toxicity monitoring.

5 In addition, I think that we need to  
6 provide -- It would be useful to provide guidelines as  
7 to what you do with dosing when you see toxicity or  
8 what you do with dosing when you don't see efficacy,  
9 if we have any of that information.

10 In terms of post marketing, this reminds  
11 me somewhat of anti-infectives. You know, we knew  
12 that penicillin worked very well for certain types of  
13 infection, but we didn't know how it worked or why it  
14 worked. We knew how it worked, but we didn't know  
15 about dynamic relationships.

16 I know that the FDA is working with IDSA  
17 to revise the guidelines now for study of anti-  
18 infective agents. Fortunately, there's been people  
19 with anti-retroviral work that have tried to elucidate  
20 some of the pharmacodynamic monitoring and the  
21 important parameters.

22 I think, for both of these agents, it  
23 would appear to me -- As I recall, for interferon it's  
24 time above  $EC_{50}$ . I think that's important. So three  
25 times a week is probably not the most optimal

1 schedule, but in terms of patient compliance maybe  
2 it's the most optimal schedule.

3 For ribavirin I think someone mentioned  
4 AUC. Maybe it's time above MIC or exposure or AUC or  
5 whatever, but we need to elucidate those things,  
6 because it would be interesting to know if the people  
7 that fail fail because of pharmacodynamics or do they  
8 fail because resistance develops because of incorrect  
9 application of pharmacodynamics; because we heard that  
10 this is a potentially curable disease earlier.

11 So it would be nice to know that. If you  
12 could optimize therapy, you actually could cure more  
13 therapy. So I think that those studies will be very  
14 important to do.

15 We didn't hear much about resistance. It  
16 sounded like that might be kind of an area that maybe  
17 we don't know too much about, but that would be, I  
18 think, another area that we should see.

19 Then post marketing and all the other  
20 things, naive patients, patients with renal disease,  
21 patients with severe liver disease -- I think all  
22 those groups need to be looked at and guidelines  
23 provided.

24 CHAIRMAN HAMMER: Thank you. Dr. Self.

25 DR. SELF: My main concern about the

1 population of patients is that the exclusion criteria  
2 that were used in the trials don't get neglected. The  
3 renal impairment patients are one group.

4 I believe those with psychiatric problems  
5 were another and, given the safety profile and the  
6 depression and some suicides, plus the fact that  
7 that's not the easiest thing to monitor, I think,  
8 might be some consideration there for an indication.

9 The issues to address post marketing: I  
10 think there might be some opportunities to get some  
11 supporting data in not too long term a fashion.  
12 Qualitatively, the data that I think would be most  
13 interesting would be data on either the stability or  
14 continued improvement in histology post treatment.

15 We've seen pretreatment to post treatment  
16 improvements, and to see that histology is not coming  
17 -- is not getting worse and is perhaps getting better  
18 is qualitatively the next step in data that I think  
19 would be -- lend some more comfort, at least to me,  
20 that this impressive suppression of virus would  
21 actually translate into clinical benefit.

22 Whether that can be built into the longer  
23 term follow-up of the trials that have been presented  
24 today or whether that's part of some post marketing,  
25 I think optimally it would be built into the follow-

1 up. There might be some feasibility issues getting  
2 another biopsy a year out, but I think every effort  
3 should be made to try and get that sort of data.

4 Finally, there's already been some  
5 discussion about exploring opportunities for  
6 retrospective studies, and that clearly will be  
7 important.

8 CHAIRMAN HAMMER: Thank you. Dr.  
9 Feinberg.

10 DR. FEINBERG: Well, I think this  
11 combination is clearly indicated for the population in  
12 which it was studied. So that, in and of itself, as  
13 others have mentioned, is a more sharply limited  
14 population of adults who have relapsed after an ALT,  
15 prior ALT response, and people without serious cardiac  
16 disease, serious psychiatric disease, and renal  
17 dysfunction, which you know, really narrows the field  
18 somewhat.

19 Obviously, drugs are always used by  
20 physicians as they see fit, but I'm not sure in a  
21 labeling sense that you can get away from the  
22 limitations imposed by how these studies were done.

23 In terms of the information to provide  
24 guidance about monitoring, I think there is certainly  
25 adequate information on the time course, the

1 development of toxicity in this study to provide  
2 guidance for clinical monitoring for routine  
3 toxicities, especially the hemolytic anemia.

4 I think, if this is not a routine kind of  
5 practice for hepatologists, then I think it is an  
6 important issue for the company to provide that  
7 education. You know, as they educate physicians in  
8 general, they will really need to explain to people  
9 that hemoglobins have to be followed and have to be  
10 followed early on, at week one and two, and then  
11 again, you know, at week three and four.

12 That seemed to be, as I recall, that it  
13 started to happen at week one, and the nadir  
14 hemoglobin occurred about one month. So I think  
15 people will really need to be educated about that.

16 The viral load monitoring has already been  
17 addressed. Post marketing studies: Again, I'm not  
18 sure I'm going to say anything that hasn't been said  
19 before me.

20 Clearly, it would be wonderful to have  
21 long term follow-up on these trial cohorts and larger  
22 cohorts for the ultimate clinical events, the late  
23 clinical sequelae that one expects from chronic  
24 hepatitis C, and also to track the duration of  
25 response, I think, would be very valuable, because

1 really we have a fairly limited period of follow-up in  
2 these trials.

3 I agree with other speakers that treatment  
4 failures should be studied. I think people mentioned  
5 a number of different dimensions, pharmacodynamics,  
6 host factors. I would really emphasize the  
7 development of resistance. We would be unwise to  
8 think that that could not occur or does not occur for  
9 hepatitis C, since it occurs for everything else.

10 I think, in a practical sense, how to  
11 treat these individuals needs to be explored. So what  
12 is an appropriate way to provide salvage therapy? Is  
13 it dose intensification? You know, how would one go  
14 about trying to treat these individuals, especially  
15 since the genotype 1 predominates anyway, and that's  
16 the more difficult aspect of the virus to treat.

17 I think that I'm concerned that we don't  
18 exactly have the optimum doses of either component in  
19 this regimen, and that has a number of sort of  
20 downstream implications. One is the impact on  
21 toxicity and how to modify toxicity.

22 The second is learning how to  
23 individualize antiviral therapy when you have a  
24 reasonable test like a viral load to follow, and I  
25 definitely think this raises issues in my mind about

1 whether this combination ought to be marketed in a  
2 fixed dose combination.

3 I guess I want to voice that I have some  
4 real concerns about doing that, because of exactly  
5 those issues, because of the need to dose modify for  
6 toxicity, because we may discover that there are  
7 different doses than the doses studied in t his trial  
8 that are optimum for different groups of patients, and  
9 because even if these are the right doses to start  
10 with, you might want to individualize treatment for a  
11 given patient.

12 So I think that -- You know, I hate to see  
13 physicians sort of locked into one way of doing this.

14 I think that probably covers most of my  
15 points.

16 CHAIRMAN HAMMER: Thank you. Dr.  
17 Hamilton.

18 DR. HAMILTON: There appears to be some  
19 unanimity of opinion as to the populations who -- for  
20 who this drug combination is indicated and those  
21 groups for whom we need more data to include them as  
22 indications. I'll not belabor that point.

23 I would like to emphasize two or three  
24 issues that have already been partially addressed, but  
25 I think they are particularly critical.

1           One is that Schering-Plough, I believe, is  
2 in a unique position as one of the leaders in  
3 antiviral chemotherapy and, therefore, it is  
4 incumbent, in my view, on their assisting in the  
5 demystification of what these parameters are that  
6 we're following.

7           They will be in the best position that I  
8 know of at least, not being a hepatologist and engaged  
9 in this all the time, but they will be, if they're not  
10 now, in a position to tell us what the meaning of  
11 these surrogate markers are, not only at baseline but  
12 long term.

13           They can provide us with objective data on  
14 how the usefulness of employing these methodologies  
15 are over time. So what does it mean if we monitor at  
16 three months? What does it mean if we get a test, and  
17 should we do all or none? That is, is undetectable  
18 the Holy Grail?

19           I think it's something to aspire to. I  
20 don't think it's very likely the only useful result,  
21 and I would like to think that the company, therefore,  
22 accesses all possible means to assist us in utilizing  
23 this data.

24           Secondly, I'd like to think that they're  
25 going to follow up this five-year cohort of volunteers

1 acidulously, and that some useful data will come from  
2 that. Rather than just being passively collected, I  
3 would hope that they would be subject to careful  
4 scrutiny.

5 Third, I'd like to think that some  
6 meaningful measures of quality of life during the time  
7 period when this drug is being given and in the  
8 immediate and long term follow-up would be done. I  
9 know, having tried this myself, it's difficult to do,  
10 but it doesn't make it any less important.

11 We're talking about people here who are  
12 about to embark upon a pretty complicated and  
13 difficult regimen, and I think we shouldn't advise  
14 that too readily without some substantial idea that  
15 it's going to be of use.

16 I guess lastly, I'd like to think that the  
17 serious adverse side effects that do occur, and there  
18 will be some of those, including deaths -- that they  
19 be followed extremely carefully and promptly, so as to  
20 identify any unanticipated longer term, more unusual  
21 adverse effects.

22 I imagine that's the charge of the FDA  
23 under any circumstances, but I would wholeheartedly  
24 support that.

25 CHAIRMAN HAMMER: Thank you. Dr. El-Sadr.

1 DR. EL-SADR: Just a couple of things. I  
2 do believe that long term follow-up is key, and would  
3 encourage the sponsors to, instead of inviting the  
4 participants at the end of the study to continue long  
5 term study, rather have it be an integral part of the  
6 study, and think ahead of time of maybe some rollover  
7 studies that nonresponders can be enrolled in to again  
8 engage them in a longer term study so we can really  
9 understand the changes that are happening  
10 histologically, as well as also virologically.

11 I found it very interesting today that the  
12 ALT was actually a pretty good mark of response, and  
13 I think that needs a little bit further investigation,  
14 because that probably is much less expensive and more  
15 available than some of the other tests.

16 Finally, I think the monitoring of the  
17 patient is going to be key, especially the anemia, but  
18 also the teratogenic/mutagenic effects with wider use  
19 of this drug in the community by a lot of different  
20 providers outside the strict criteria of a clinical  
21 trial. So I think a lot of education and training of  
22 the providers needs to happen.

23 On the other hand, it's a wonderful  
24 opportunity, because probably a lot of this  
25 combination will be used extensively, and it may be an

1 opportunity for the sponsor to learn an awful lot  
2 about maybe more efficient ways to monitor the  
3 patients, as well as also to try to develop some real  
4 good training materials for patients and for their  
5 providers.

6 CHAIRMAN HAMMER: Thank you. Dr.  
7 Pomerantz.

8 DR. POMERANTZ: Yes. I think this is very  
9 exciting as a virologist finally seeing a variety of  
10 drugs in the last few years start to work on viruses.

11 First to address the questions, I agree  
12 with virtually everything that was said here.  
13 Question number two, it's a very limited group of  
14 people where the indications are going to be actively  
15 supportable, and those are the previous responders to  
16 interferon.

17 Clearly, the next question -- I would just  
18 reiterate that hemoglobin and hematocrit may not be  
19 evaluated as often by our clinical hematologists as  
20 Dr. Friedman talks about, as it should be now with  
21 this regimen. So that should be underlined.

22 I think, when it comes to viral RNA, more  
23 often is better than less often in this regard,  
24 because again we'd like to see, especially those where  
25 it becomes undetectable, whether this re-presents

1       itself rather -- in a short amount of time rather than  
2       have the patient come back in a year and find out that  
3       they've now redeveloped viremia.

4                 Then what I think is the most interesting  
5       question, which is the addressing the post marketing -  
6       - I think you can divide this up into two groups, and  
7       one of them is clinical. The other is more basic  
8       science that then will lead back into the clinics.

9                 Clinical:       Clearly, people have  
10       reiterated, and I believe very strongly that even  
11       though the indication will probably be very limited,  
12       there will be a lot of up front use of these drugs, as  
13       was alluded to.

14                Someone comes in with hepatitis C. A  
15       variety of physicians are going to be pushed to use  
16       both of these agents up front. Clearly, the other  
17       group are those that, as we've talked about, that do  
18       not respond to interferon, even if they're given the  
19       chance.

20                We hear that there are studies going on.  
21       Hopefully, post marketing, there will be more studies  
22       going on in this group. Then the other group that  
23       I've mentioned earlier that's a big interest to me are  
24       those that are dual infected with HIV I and HCV.

25                Clearly, you have to be very careful,

1 since we've made remarkable inroads in HIV, and you  
2 can no longer be a therapeutic nihilist, that you are  
3 not stealing from Peter to pay Paul. So I think that,  
4 when you're treating now with HIV and HCV, I'm looking  
5 forward to finding what the Amfar group finds on at  
6 least the initial studies of these two.

7 When you go into the science, I agree with  
8 Dr. Gretch. I think that RNA levels are very  
9 different, depending on the technique and the  
10 quantitation. Do you want sensitive? Do you want  
11 ultra sensitive? Do you want really ultra sensitive?

12 Well, I think it depends on what you're  
13 asking the test to tell you. If you're looking for a  
14 response, then clearly the test that's now out there  
15 that's being used by Schering-Plough is enough.

16 If you're looking for eradication, whether  
17 you want to make the analogy to retrovirus or not, I  
18 said when I chaired the session on latency at the  
19 Chicago Retroviral meetings that close only counts for  
20 hand grenades and horse shoes. I think that that  
21 holds as well for an RNA virus.

22 So if you're looking in your post  
23 marketing for eradication -- and we'll keep our  
24 fingers crossed that Dr. Gretch is right in that  
25 regard -- then ultra sensitive tests, as low as you

1 can get within the linear amplification range may not  
2 be just a scientific -- a little piece of moving tests  
3 around, but be very important in trying to  
4 prognosticate the question of eradication.

5 I also think that it's important, as Dr.  
6 Hamilton said, that eradication is not everything  
7 here. So for other treatment parameters that fall  
8 short of eradication but still affects the natural  
9 prognosis of disease, then again the level of RNA will  
10 have to be adjusted accordingly in the studies that  
11 are done.

12 So what I'm saying is that the tests have  
13 to fit the questions that you are asking it to do.

14 Then finally, as was brought up a few  
15 times here, I think by Dr. Zimmerman and others, the  
16 liver RNA level is very important. Clearly, not only  
17 in the hepatocytes but maybe in the monocyte  
18 macrophages, even at very low levels, you are looking  
19 for -- especially in some of these people with no HCV  
20 in their blood, you are looking for the question of  
21 areas of low level persistent infection that will then  
22 -- have the potential to then reseed the rest of the  
23 liver and the body.

24 So there liver viral RNA is going to be  
25 very important and should be placed in a number of

1 your upcoming studies. Thank you.

2 CHAIRMAN HAMMER: Thank you. Dr. Lipsky.

3 DR. LIPSKY: Thank you. The question  
4 about the population of patients with which the safety  
5 and efficacy was supported, I think, has been  
6 adequately addressed by the other members of the  
7 committee.

8 On the issue of monitoring, what hasn't  
9 been stated is the ribavirin itself and where is that  
10 role. Of course, in background to that is we don't  
11 even know the mechanism of its effect, but it's  
12 pleasing to hear that there is large departments for  
13 both antivirals and immunology at the company and, I'm  
14 sure, many other people looking into that.

15 Certainly, understanding the relationship  
16 of the level of the drug, if any, to the effect and  
17 also we don't know much about the dose, but the  
18 company is telling us that that information is  
19 ongoing, and they are to be lauded for that.

20 As mentioned briefly before this committee  
21 was taken to task, at least with HIV drugs with the  
22 failure to look at pediatric populations and besides  
23 pediatric populations many others that could come to  
24 mind.

25 Finally, you know, what issue must be

1 addressed post marketing. Probably one of the most  
2 crucial ones, which has been alluded to before, is  
3 simply have we seen some patients who were cured of  
4 their infection by this treatment.

5 CHAIRMAN HAMMER: Thank you. I'll just  
6 make a few comments. Most of my thoughts have already  
7 been very eloquently stated. I'm not going to restate  
8 what population this has been demonstrated in. I  
9 think that's fairly clear, and that's what the label  
10 should be restricted to.

11 I would reiterate that the warnings on the  
12 label have to be regarding anemia, cardiac disease,  
13 psychiatric issues and pregnancy, because, remember,  
14 there were strict criteria for entry into this study,  
15 and there were still a couple of suicides.

16 As this combination gets more widely,  
17 these will be issues, and I think the label and how it  
18 specifically -- how the warnings are placed will be  
19 very critical as to whether they're picked up by  
20 treating physicians in a broad fashion, and I'll come  
21 back to that later.

22 As far as the monitoring, I think it's  
23 fairly clear, and I think it can be reasonably well  
24 done, to educate physicians and patients about the  
25 anemia issues. Clearly, the virologic monitoring, the

1 one important parallel with HIV is that investigator,  
2 clinician and patients as stimuli to assay developers  
3 and the agency are all important in moving these  
4 things forward as standards of care, and that model,  
5 I think, needs to be used, and I would repeat --  
6 reiterate what Dr. Pomerantz said about virologic  
7 monitoring.

8 It's clearly going to get more frequent in  
9 this disease and should get more frequent in this  
10 disease as we have quality controlled assays and  
11 predictors of response get more well defined.

12 Dr. Bertino's statements about PK  
13 parameters and pharmacodynamic parameters leads to a  
14 question that this committee always brings up but  
15 never quite answers is the issue of is there a role  
16 for some sort of PK parameter therapeutic drug level  
17 monitoring, etcetera.

18 I think it's even more hazy with these two  
19 agents as far as what interferon levels might or might  
20 not mean, and certainly what ribavirin, either red  
21 cell levels or poor plasma levels mean. That does not  
22 mean, however, that we shouldn't try to understand  
23 this a little bit better, both for efficacy and safety  
24 reasons; but I think the PCR test is clearly the most  
25 important thing to have out there in a way, that's

1 standardized and quality controlled.

2 As far as the post marketing issues, most  
3 of these things have been very clearly stated. I  
4 would just break it down to a few things very quickly.

5 The populations -- I'm happy to see that  
6 there are a number of studies in place or planned for  
7 interferon naive subjects. That's going to be the  
8 most important new dataset and, hopefully, we'll see  
9 good responses and perhaps expanded label indications.

10 The interferon nonresponders, the HIV  
11 population, post transplant, pediatric and, perhaps  
12 most importantly, those individuals with some level of  
13 organ -- a greater level of organ dysfunction that  
14 were represented in this study because of the ratio of  
15 toxicity to efficacy may well shift, particularly in  
16 those with greater degrees of renal dysfunction; but  
17 it would be also very important to know in those with  
18 greater degrees of hepatic dysfunction what this  
19 combination can do.

20 There are also the issues of duration of  
21 therapy which are being addressed, and probably need  
22 to be refined further, the issue of dose and genotype  
23 that have already been talked about, and I would  
24 really urge investigators and the sponsor working  
25 together to come up with more clear on-treatment

1 predictors of response than a single value of the RT  
2 PCR down the road.

3 So I think we need really refinements  
4 perhaps even within the first four to eight weeks, and  
5 even the first four to six weeks of treatment, because  
6 we'll save a lot of money and avoid potential  
7 toxicities if we know what we're doing and have  
8 predictors of response later.

9 As far as how to study things, it can be  
10 broken down, I think, into the clinical trials that  
11 are needed and are ongoing and epidemiologic studies.  
12 That's already been mentioned.

13 I would reiterate that the pathogenesis of  
14 this disease is now a nicely wide open field, and  
15 another parallel is that, once you have semi-effective  
16 and -- you know, we need more effective agents than  
17 this combination, but it's a very good start -- is the  
18 probing of the system, as was seen as another  
19 important parallel. I think that goes for any viral  
20 disease with a reasonable turnover rate, that you can  
21 understand a lot more about what's happening  
22 virologically and immunologically when you perturb the  
23 system, and I think we all understand that paradigm.

24 The mechanisms of these agents -- One  
25 could go on for several days, but the essential issue

1 is we don't really understand it, and there's a lot of  
2 basic science that needs to go on there and,  
3 obviously, the resistance issues will arise, as Dr.  
4 Feinberg mentioned, and we need to be ahead of that  
5 game with viral sequencing and to understand things  
6 through basic science.

7 The other aspect of the clinical trials is  
8 the treatment of the populations we talked about.

9 The epidemiologic studies, I think, fall  
10 into the long term follow-up of the current trials,  
11 and I would urge the more active, long term follow-up  
12 of individuals rather than the passive system and the  
13 self-selection that will go on to just follow  
14 responders later.

15 That will give us important information as  
16 far as do the markers we see now translate into long  
17 term outcome; but if we -- if the patients' group is  
18 too selected, we'll have questions that remain open.

19 I think an active system is important,  
20 both for the outcome issues of cirrhosis, cancer,  
21 transplantation and death, as well as the safety  
22 issues and the pregnancy issues, again, that we've  
23 talked about.

24 One thing might be worth thinking with  
25 investigator groups, working with the sponsor and the

1 agency, are registries that can be set up now to look  
2 at these long term outcomes, the toxicity issues and,  
3 particularly, the pregnancy issue.

4 Lastly, physician and patient education,  
5 I don't think, can be underestimated as to their  
6 importance, but I think that's something we've seen  
7 that can be done in viral disease with good benefit.

8 One advantage here is that treatment of  
9 this disease is already in the hands of specialists,  
10 and so that I think that's helpful as far as  
11 protection of patients, and it will likely remain  
12 under the guise of hepatologists, and it may even  
13 spread to infectious disease physicians -- who knows?  
14 -- in the future.

15 With that, I don't have any additional  
16 comments. I would just ask Dr. Jolson whether we've  
17 addressed everything from the agency's perspective.  
18 We're ahead of schedule. So we certainly have the  
19 opportunity, if needed, to open things up and make  
20 sure we've probed everywhere that yo wish us to go.

21 DR. JOLSON: I think -- Since you're ahead  
22 of schedule --

23 CHAIRMAN HAMMER: We would never want to  
24 end early.

25 DR. BEHRMAN: Right. Well, you can take

1 up an hour and a half.

2 One thing that we mentioned before -- The  
3 design of trials in this field is obviously very  
4 complex, and since we don't always have you present,  
5 are there any other comments you'd like to make or  
6 advice you'd like to give to us when we're negotiating  
7 with sponsors in discussion design.

8 I think Dr. Self mentioned maybe biopsy is  
9 a little more remote. Dr. Hamilton mentioned looking  
10 in the liver. There was discussion of quality of  
11 life. We had brought up before the issue of -- or you  
12 had -- the committee had brought up using a two point  
13 difference in the scale. Is that appropriate? Are  
14 there other things we should be thinking about or do  
15 you want to add additional comments on any of those  
16 issues?

17 CHAIRMAN HAMMER: First, let me ask the  
18 committee members if there is -- I think the question  
19 is do we have any suggestions. We've talked in  
20 generalities about the study designs that should go  
21 forward in a post marketing or current phase, and do  
22 we have specific suggestions about how really to  
23 monitor patients in these trials or how the designs  
24 should be constructed.

25 DR. BEHRMAN: Or some future trials of

1 future agents.

2 DR. MURPHY: If I could word it just a  
3 little differently, I think the company did a noble  
4 job today. Where we were when we put -- you know,  
5 when we were looking at the disease, as we talked  
6 about not having answers for decades, and put together  
7 two trials that you saw today.

8 What Rachel is asking is we are now  
9 further along in our knowledge. What would you like  
10 to see that you didn't see in future study designs?  
11 That's what we're sort of asking.

12 CHAIRMAN HAMMER: I guess I'll start.  
13 First of all, I think for any future -- The current  
14 sponsor that may be a future sponsor or other future  
15 or other future sponsors, one other analogy, and not  
16 to overdraw this, is that the bar gets set higher with  
17 every -- with the progress that we make, and that's  
18 true for the field. That's true for this committee,  
19 probably true for the agency as well.

20 This is really a step forward in this  
21 particular population that was studied, from  
22 essentially no response to a good 40-45 percent  
23 response.

24 I think the things that are going to  
25 evolve will be a greater understanding of the

1 pathogenesis of the disease naturally, and that has to  
2 be pushed in the setting of therapeutic agents. So  
3 pathogenetically based trials, either nested within  
4 larger treatment trials or free standing, should be  
5 there.

6 We're going to want to see, I think -- We  
7 pressed a little bit for it, but I think the issues of  
8 assays and their performance and their quality control  
9 and quality assurance will be very important. The  
10 tissue based virology is going to be clear, and  
11 probably the next time around we're going to actually  
12 want to see what's happening in the liver at the time  
13 of the presentation.

14 The histologic issues in the long term, as  
15 Dr. Self mentioned, I think, are critical. It depends  
16 when that application comes through.

17 I think it's a little hard to think about  
18 novel designs in studies yet, but that will likely  
19 come as we proliferate the number of agents and  
20 combinations and alternatives come forward, but I  
21 think the issues are understanding the virology a bit  
22 more, the immunology a bit more, mechanisms of actions  
23 of the drugs that come before us, and pinning down the  
24 virologic response, both in the periphery and in the  
25 tissues.

1 DR. SELF: I guess I would add to that,  
2 though. I mean, we have this discussion that the  
3 clinical endpoints are too far out to really be  
4 feasible. I think the studies that have been  
5 conducted are -- were very nicely done, but they're  
6 perhaps at the other end of the spectrum with  
7 evaluations coming fairly shortly after the cessation  
8 of treatment, and not having really enough information  
9 about -- longitudinal information on histology, which  
10 is the main thing we're going to be hanging onto  
11 clinically.

12 So when I would think of other study  
13 designs in addition to those elements that you  
14 described, I would also like to see a little longer  
15 follow-up and more emphasis on endpoints that are  
16 measured post cessation of treatment.

17 CHAIRMAN HAMMER: I think we also should  
18 remember we're hampered a bit by the hep C systems we  
19 have to work with and, as those evolve, also  
20 mechanisms of actions of drugs and drug development  
21 wills be fostered substantially.

22 Dr. Bertino?

23 DR. BERTINO: One of the things -- I think  
24 we sometimes get hung up on the labeling, and I think  
25 that we need to integrate our in vitro data, our

1 pharmacodynamic data, our kinetic data in these  
2 ongoing studies.

3 I mean, it might be very interesting to  
4 look at a continuous infusion, interferon with  
5 ribavirin dosed -- I don't know -- some other way or  
6 the way it's being dosed now or something like that.  
7 But you know, you can use hollow fiber models for some  
8 of these viral things and actually come up with  
9 dynamic data, and then try to go into your biologic  
10 model.

11 I think the companies that are developing  
12 the anti-retrovirals are realizing this. Some people  
13 have really been doing this analysis. So I think, for  
14 future studies, not just in hep C but in viral agents,  
15 it would be nice to start integrating all these  
16 things.

17 We've got to put the cart before the  
18 horse, you know. Yeah, this works three times a week.  
19 So that's how we're going to study it, but --

20 CHAIRMAN HAMMER: Dr. Hamilton.

21 DR. HAMILTON: In my opinion, the one  
22 inviolable precept of doing a clinical trial is to  
23 keep your eye on the ball. You cannot do too much.  
24 Otherwise, you'll come up empty.

25 Clearly, no one is asking me what trials

1 need to be done in the area of hepatology, and only  
2 indirectly, I guess, are they asking you. In that  
3 role, I assume that we can serve some purpose in  
4 identifying those gaps in the regimens that are  
5 currently being employed.

6 You know, to that end, it would be helpful  
7 to me to incorporate some process by which I became  
8 prospectively more informed about this topic. I hate  
9 to say it, but I'm not really an expert in this field.

10 There may be five or ten or 50 other  
11 studies out there that it would be useful for me to  
12 know the results of, or at least to have some greater  
13 familiarity.

14 Yes, we have a broad representation here,  
15 but it seems to me that's a little bit different, and  
16 perhaps a prospectively identified -- I don't know --  
17 bibliography or conference call -- I don't know --  
18 something that would prepare me better, I think, would  
19 be useful.

20 CHAIRMAN HAMMER: Dr. Lipsky.

21 DR. LIPSKY: Finally, one of the issues  
22 that seemed most intriguing was this importance of the  
23 early response for the sustained response. Although  
24 there was a trial that would address this in part, I  
25 believe that it was just by having a longer duration

1 of time.

2 It would seem that, if one had a more  
3 formal study that said, all right, this is when this  
4 patient converts, if you will, to negative, and then  
5 go from there and say, all right, we need X length of  
6 therapy from that period of time, based on what Dr.  
7 Gretch said, to have a sustained eradication, that  
8 that would be something reasonable.

9 In other words, how do we -- For those  
10 patients -- and unfortunately, they're not all the  
11 patients, but those patients who appear to be heading  
12 for a good response, how do we maximize that, and how  
13 do we make that prolonged.

14 I would look to that as being more  
15 formally addressed, and I'm not certain that any of  
16 the trials that were mentioned specifically looked at  
17 that point, because that appears to be the major  
18 variable, the duration of therapy once conversion is  
19 done.

20 Related to that is, is there something  
21 that one can look back at and say in those patients  
22 who did better, were the drug levels better? I mean,  
23 do we know that? What was that information? Did they  
24 have better levels of ribavirin? Were they lowered?  
25 Where did the interferon go? What were the other

1 immunologic markers that were looked at?

2 I presume there is a ton of data that,  
3 you know, we haven't seen and could be ferreted out,  
4 but I think something more formally that looks at  
5 control of the therapy and, more precisely, its  
6 duration for its maximum effect --

7 CHAIRMAN HAMMER: Is that okay?

8 Well, then thank you. I'd like to thank  
9 the panel members. I'd like to thank the members of  
10 the audience and the agency, and particularly the  
11 sponsor today. Thank you.

12 This session is closed.

13 (Whereupon, the foregoing matter went off  
14 the record at 3:35 p.m.)

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C E R T I F I C A T E

This is to certify that the foregoing transcript in  
the matter of:            Meeting of the  
                                 Antiviral Drugs Advisory Committee

Before:                    DHHS/FDA/CDER  
Date:                      May 4, 1998  
Place:                      Gaithersburg, MD

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