

FOOD AND DRUG ADMINISTRATION 11 19 52  
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF  
THE ANTIVIRAL DRUGS ADVISORY COMMITTEE

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8:25 a.m.

Wednesday, December 12, 2001

Versailles Room  
Holiday Inn  
8120 Wisconsin Avenue  
Bethesda, Maryland

## ATTENDEES

## COMMITTEE MEMBERS:

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## ATTENDEES (Continued)

## COMMITTEE MEMBERS: (Continued)

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## ATTENDEES (Continued)

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## VOTING PATIENT REPRESENTATIVE:

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## NON-VOTING GUEST:

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## ATTENDEES (Continued)

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DAVE GREEN, PH.D.  
LOUIS MARZELLA, M.D., PH.D.  
WILLIAM SCHWIETERMAN, M.D.  
JAY SIEGEL, M.D.  
KAREN WEISS, M.D.

## SCHERING-PLOUGH REPRESENTATIVES:

DR. JANICE K. ALBRECHT  
DR. MARIELLE COHARD  
DR. PENELOPE J. GILES  
DR. KENNETH KOURY  
DR. MARK LAUGHLIN  
DR. JOHN MCHUTCHINSON

## ALSO PRESENT:

MR. BRIAN KLEIN  
MR. JULES LEVIN  
KATHLEEN SCWHARZ, M.D.

## C O N T E N T S

## TOPIC:

An update on the approval of  
 BLA 103949/5002, PEG-Intron  
 (PEG-interferon alfa-2b) powder for injection,  
 indicated for use alone or in combination with  
 Rebetol (ribavirin, USP) for the treatment of  
 chronic hepatitis C in patients with compensated  
 liver disease who have not been previously treated  
 with interferon alpha and are at least 18 years of age

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

(8:25 a.m.)

1  
2  
3 DR. GULICK: Good morning. I was going to ask  
4 people to take their seats, but it looks like everyone  
5 already has, which is a good sign to say that I guess we  
6 can get started.

7 I'm Trip Gulick from Cornell, and I'd like to  
8 open this meeting of the Antiviral Drugs Advisory  
9 Committee.

10 For those of you who were at the last one,  
11 we've taken great pains to look at the plumbing system in  
12 this hotel.

13 (Laughter.)

14 DR. GULICK: And everything checks out really  
15 well, so I don't think we'll have any worries today.

16 I'd like to start by having the committee  
17 introduce themselves. Please state your name and where  
18 you're from, and we'll start with Dr. Sun over at this end.

19 DR. SUN: Eugene Sun, Abbott Laboratories.

20 DR. HOOFNAGLE: I'm Jay Hoofnagle from NIDDK at  
21 the NIH.

22 DR. SEEFF: Leonard Seeff from NIDDK and the  
23 VA.

24 DR. RODVOLD: Keith Rodvold, University of  
25 Illinois at Chicago.

1 MR. MARCO: Michael Marco, Treatment Action  
2 Group in New York.

3 DR. DeGRUTTOLA: Victor DeGruttola, Harvard  
4 School of Public Health.

5 DR. SCHAPIRO: Jonathan Schapiro, Stanford  
6 University.

7 DR. TURNER: Tara Turner, Executive Secretary  
8 for the committee.

9 DR. WOOD: Lauren Wood, National Cancer  
10 Institute, NIH.

11 DR. ENGLUND: Janet Englund, University of  
12 Chicago.

13 DR. WONG: Brian Wong, West Haven, Connecticut,  
14 VA and Yale University.

15 DR. KUMAR: Princy Kumar, Georgetown  
16 University.

17 DR. MATHEWS: Chris Mathews, University of  
18 California, San Diego.

19 DR. SCHWIETERMAN: Bill Schwieterman, Center  
20 for Biologics, FDA.

21 DR. GREEN: Dave Green, clinical trials, FDA.

22 DR. WEISS: Karen Weiss, Center for Biologics,  
23 Food and Drug Administration.

24 DR. SIEGEL: Jay Siegel, Center for Biologics.

25 DR. GULICK: Thank you, and by teleconference,

1 | we have Dr. Stanley.

2 |           DR. STANLEY: Hello. Dr. Sharilyn Stanley,  
3 | Texas Department of Health.

4 |           DR. GULICK: Very good. We can hear you well.  
5 | Can you hear us well? I guess you can.

6 |           DR. STANLEY: Pretty good.

7 |           DR. GULICK: Thanks.

8 |           Tara Turner will now read the conflict of  
9 | interest statement.

10 |           DR. TURNER: The following announcement  
11 | addresses conflict of interest with regard to this meeting  
12 | and is made a part of the record to preclude even the  
13 | appearance of such at this meeting.

14 |           Based on the submitted agenda for the meeting  
15 | and all financial interests reported by the committee  
16 | participants, it has been determined that all interests in  
17 | firms regulated by the Center for Drug Evaluation and  
18 | Research present no potential for an appearance of a  
19 | conflict of interest at this meeting with the following  
20 | exceptions.

21 |           In accordance with 18 U.S.C. 208(b)(3), full  
22 | waivers have been granted to Dr. Keith Rodvold and Dr.  
23 | Jonathan Schapiro which allow their participation  
24 | concerning Biologics License Application 103949-5002, PEG-  
25 | Intron, sponsored by Schering-Plough.

1           A copy of these waiver statements may be  
2 obtained by submitting a written request to the agency's  
3 Freedom of Information Office, room 12A-30, Parklawn  
4 Building.

5           In accordance with section 505(n)(4) of the FDA  
6 Modernization Act, Dr. Princy Kumar would like to disclose  
7 that she owns stock in a competing firm. The value of the  
8 stock is less than \$5,000.

9           We would also like to disclose for the record  
10 that Dr. Jonathan Schapiro and Dr. Victor DeGruttola have  
11 interests which do not constitute financial interests  
12 within the meaning of 18 U.S.C. 208(a), but which could  
13 create the appearance of a conflict. The agency has  
14 determined, notwithstanding these interests, that the  
15 interests of the Government in their participation  
16 outweighs the concern that the integrity of the agency's  
17 programs and operations may be questioned.

18           In addition, Dr. Eugene Sun from Abbott  
19 Laboratories is participating in this meeting as an  
20 industry representative acting on behalf of regulated  
21 industry. As such, he has not been screened for any  
22 conflicts of interest.

23           Further, with respect to FDA's invited guests,  
24 Dr. Jay Hoofnagle, an employee of the National Institute of  
25 Diabetes and Digestive and Kidney Diseases, has received

1 clearance from his ethics office to participate in today's  
2 meeting.

3 In the event that the discussions involve any  
4 other products or firms not already on the agenda for which  
5 an FDA participant has a financial interest, the  
6 participants are aware of the need to exclude themselves  
7 from such involvement, and their exclusion will be noted  
8 for the record.

9 With respect to all other participants, we ask  
10 in the interest of fairness that they address any current  
11 or previous financial involvement with any firm whose  
12 products they may wish to comment upon.

13 I have one announcement. I would like to note  
14 for the record that our consumer representative, Dr.  
15 Courtney Fletcher, had to cancel his participation in this  
16 meeting at the last minute and there was no time to replace  
17 him. We are, however, fortunate to have Michael Marco  
18 present as our patient representative to provide that  
19 special point of view. Thank you.

20 DR. GULICK: Thanks very much.

21 I'd like to call on Dr. Weiss for a few  
22 introductory comments.

23 DR. WEISS: Yes. I just want to welcome the  
24 committee members, our invited guests, and the public to  
25 this meeting and to let people know that the purpose of

1 | this meeting is to review and educate the committee and the  
2 | public on the data supporting the safety and efficacy of  
3 | the combination of pegylated interferon plus ribavirin for  
4 | use in patients with chronic hepatitis C. That license  
5 | application was approved by the Center for Biologics in  
6 | August of this past year, and we believed it would be  
7 | appropriate to update the committee on the database, as  
8 | well as to inform the committee and the public about the  
9 | issues that were left outstanding at the time of the  
10 | approval that have resulted in a number of phase IV or  
11 | postmarketing commitments, studies that are either planned  
12 | or ongoing. So, we hope that with this presentation, we  
13 | will just provide that information to the committee and to  
14 | the public. I look forward to the presentations and the  
15 | discussion.

16 | DR. GULICK: Thank you.

17 | So, we'd like to start with the sponsor  
18 | presentation from Schering Corporation. Dr. Giles?

19 | DR. GILES: Thank you, Dr. Gulick. Allow me to  
20 | introduce myself. My name is Penny Giles from the  
21 | Regulatory Affairs Department at Schering-Plough. We at  
22 | Schering are pleased to be invited here to provide this  
23 | committee an update on our progress since we were last here  
24 | in 1998.

25 | Prior to 1998, the only therapies available for

1 the treatment of chronic hepatitis C were alpha  
2 interferons. Sustained virological response was low when  
3 Intron A was given for a 24-week period. We showed that by  
4 extending the duration of treatment to at least 48 weeks,  
5 that sustained response rate could be more than doubled.

6 When we were last here, we showed the data that  
7 when Rebetol was combined with Intron A, that same  
8 virological response rate of 41 percent could be obtained.  
9 This new combination therapy was a big step forward in the  
10 treatment of chronic hepatitis C.

11 Since that time, we have developed a pegylated  
12 interferon which has improved the same virologic response  
13 over that of the normal interferon, and today we will be  
14 talking about the addition of Rebetol to PEG-Intron which  
15 results in a sustained response rate of 52 percent.

16 The analysis that we will be presenting today  
17 shows that a 61 percent sustained virologic response rate  
18 is attainable if the ribavirin dose is weight-adjusted.

19 I'd like to introduce our primary speaker  
20 today, Dr. Janice Albrecht from Clinical Research, Dr.  
21 Garaud from Clinical Research, Dr. Koury from  
22 Biostatistics, and Dr. Laughlin from Clinical Pharmacology.

23 We also have with us today consultants: Dr.  
24 John McHutchinson from Scripps Clinic. Dr. McHutchinson  
25 will say a few words at the close of our presentation about

1 | some of the risk/benefit decisions confronting physicians  
2 | in choosing to treat hepatitis C patients. Also with us is  
3 | Dr. L.J. Wei from Harvard, Biostatistics, who has helped us  
4 | with some of the analyses that we have done on the data  
5 | that we will be presenting.

6 |           With that, I'd like to turn the floor over to  
7 | Dr. Albrecht.

8 |           DR. ALBRECHT: Thank you, Dr. Giles, Mr.  
9 | Chairman, members of the committee.

10 |           The therapeutic goal of the treatment of  
11 | chronic hepatitis C is the eradication of the virus and a  
12 | sustained virologic response that will result in the halt  
13 | of the disease. Until recently Intron A plus Rebetol was  
14 | the treatment standard for chronic hepatitis C.

15 |           Recently we have shown with PEG-Intron plus  
16 | Rebetol that the efficacy can be increased, and as Dr.  
17 | Weiss noted, this was licensed, approved in August of this  
18 | year. The indication is treatment of chronic hepatitis C  
19 | in treatment-naive adults. The approved dose is PEG-Intron  
20 | 1.5 once weekly plus Rebetol 800 milligrams per day for 48  
21 | weeks.

22 |           The committee has been provided as background  
23 | the key publications on the use of Intron A plus Rebetol,  
24 | PEG-Intron monotherapy, and PEG-Intron plus Rebetol.

25 |           The PEG-Intron molecule is created from a

1 combination of the parent, which is interferon alfa-2b.  
2 The molecule is achieved by attaching a 12,000 Dalton  
3 polyethylene glycol molecule which is straight chained to  
4 the alfa-2b molecule. The result of this attachment of the  
5 PEG molecule extends the half-life to approximately 40  
6 hours compared to 3.6 hours with the parent molecule. What  
7 we achieve with this extension of the half-life is the  
8 ability to dose once weekly.

9           During the development program with PEG-Intron,  
10 we looked at our Intron database for the parent compound  
11 which is administered as a single dose 3 million units  
12 three times a week. We knew from the literature and from  
13 our own database that patient weight had an influence on  
14 sustained response when we use a flat dose of Intron A.  
15 What we found out when we did logistic regression on our  
16 database was that weight of the patient was a significant  
17 factor, and one of the questions we ask ourselves is should  
18 we weight-base our PEG-Intron.

19           When we look at our 800-patient database of  
20 Intron A monotherapy at 3 million units three times a week,  
21 all patients receiving the same dose, what we find are  
22 patients that weigh less, those small patients less than 55  
23 kilos, those patients 75 to 55 have really quite a good  
24 response with monotherapy, 19 to 25 percent, as opposed to  
25 the rather low response rates that we see in those patients

1 who weigh more, in particular more than 75 kilos.

2           The take-home message from this analysis for us  
3 was that one size doesn't fit all, and therefore we made a  
4 decision to weight-base our dosing of PEG-Intron. We dose  
5 PEG-Intron by microgram per kilogram dosing. Our phase I  
6 kinetic studies were done that way, and we then moved on to  
7 look at the safety and efficacy of PEG-Intron as  
8 monotherapy.

9           We conducted a large dose definition study,  
10 1,219 patients. We compared three doses of PEG as weight-  
11 based dosing -- .5 micrograms per kilogram once weekly; PEG  
12 1.0 micrograms per kilogram once weekly; and PEG 1.5  
13 micrograms per kilogram once weekly -- to, at that time,  
14 the standard of care, which was Intron A, 3 million units  
15 three times a week. All patients were treated for 48  
16 weeks, and they were followed for an additional 24 weeks  
17 when they completed their therapy.

18           The primary endpoint in the study was sustained  
19 loss of HCV RNA 24 weeks following the end of treatment.

20           I'd now like to show you the data that we saw  
21 during the course of the study. The y axis is the percent  
22 of patients that were HCV RNA negative using the National  
23 Genetics Institute assay, which has a lower limit of  
24 detection of 100 copies. For all of the subsequent data  
25 that I will show you, we have used the National Genetics

1 Institute assay, and all studies were done by the same lab.

2 Across the bottom are the treatment weeks. As  
3 you can see, throughout the treatment period at the  
4 sampling times, 4, 12, 24, 36, and 48, the end of  
5 treatment, the three PEG doses, 1.5, 1.0, and .5, were  
6 superior to the Intron A 3 million units three times a  
7 week. At the end of the treatment period, the highest  
8 response rate was in the 1.5 dose.

9 However, with the alpha interferons as  
10 monotherapy, we're very much aware of the problem with  
11 relapse. In fact, relapse is about 50 percent, and it was  
12 when we added ribavirin to Intron A that we could decrease  
13 the relapse.

14 So, not surprisingly, what we saw was a very  
15 high relapse when we took these patients off drug. What  
16 was surprising is the 1.5 dose had essentially the same  
17 efficacy as the 1.0 dose. We tried to understand why this  
18 had happened, and what we really found and the best  
19 explanation we have is that in this increased response rate  
20 during therapy, there were more patients who were HCV-1  
21 that actually responded. However, when we took these  
22 patients off of therapy, we had a higher relapse rate in  
23 the 1.5. 66 percent of the patients relapsed in the 1.5  
24 dose as compared to 46 in the 1.0 dose.

25 The next thing we wanted to do is take a look

1 at this study. As I told you earlier, we did a  
2 multivariate analysis on our Intron A monotherapy study,  
3 and what we found is that weight was a predictive factor.  
4 We did the same thing on this study trying to see if indeed  
5 we had a limited weight as the confounder when we use  
6 weight-based dosing with PEG.

7 What we found was that the significant factors  
8 associated with sustained virologic response were, not  
9 surprisingly, genotype and viral load. These are things  
10 that are well-known with the treatment of chronic hepatitis  
11 C; not surprising, the absence of cirrhosis or bridging  
12 fibrosis, and age has also been reported, younger ages with  
13 the patients responding better. What we did see is that  
14 body weight was no longer predictive. So, we appeared to  
15 have taken care of the confounding factor of weight when we  
16 dose on a microgram per kilogram basis.

17 The next slide shows you the doses that we  
18 selected for use in combination with Rebetol. I will  
19 comment prior to initiating the trial, I'm going to  
20 describe we did combination toxicology in monkeys, we did  
21 phase I studies to look at pharmacokinetics and assure  
22 ourselves that ribavirin in combination with PEG-Intron was  
23 appropriate to go forward. These were small studies and we  
24 won't take the time today to discuss them.

25 We selected our doses to be used with Rebetol

1 at 24 weeks of treatment in the PEG-Intron study. We  
2 selected 1.5 micrograms per kilogram because it had the  
3 maximum antiviral activity at that time point and also  
4 because we saw this heightened activity in the HCV-1  
5 patients. We selected a low dose. We selected the .5  
6 microgram per kilogram dose because it looked very much  
7 like Intron A and it seemed to be better tolerated, and we  
8 thought perhaps that we would, indeed, have a regimen that  
9 was equivalent to Intron or maybe even slightly better.

10 I'd now like to describe the study on which the  
11 license is based. This is a study comparing the standard  
12 of care at that time, Intron A 3 million units three times  
13 a week with 1,000 to 1,200 milligrams of ribavirin  
14 administered daily. The basis for the ribavirin dose was  
15 patient weight. Those weighing less than or equal to 75  
16 kilos received 1,000; those weighing more than 75 kilos  
17 received 1,200.

18 The first regimen that we looked at with PEG-  
19 Intron plus Rebetol was basically an induction regimen. In  
20 this regimen we used the high dose, 1.5 micrograms per  
21 kilogram once weekly for 4 weeks. We followed it by the  
22 low dose, .5 microgram per kilogram once weekly for 44  
23 weeks. The ribavirin dose administered was the same as is  
24 with the Intron A regimen.

25 The basis for this regimen was the fact that in

1 | the literature at the time and in our own databases, we  
2 | knew that if you used high-dose daily interferon, you would  
3 | see a very, very rapid decrease in the HCV rate, and what  
4 | you would see is a very early negative response with high-  
5 | dose interferon. What we were trying to do is to get the  
6 | patients to become HCV negative and then maintain them on a  
7 | lower dose. As you'll see later, this induction strategy  
8 | is really not effective.

9 |           The third arm in the study was PEG-Intron 1.5  
10 | micrograms per kilogram administered once weekly with  
11 | Rebetol at a dose of 800 milligrams. All patients received  
12 | the same dose of Rebetol.

13 |           As we look back, hindsight is 20/20. We  
14 | selected the 800 milligram dose of Rebetol because there  
15 | was some concern that there might be an additive toxicity  
16 | with a higher dose of PEG with that very high dose of  
17 | ribavirin. And in fact, as I will show you later, I think  
18 | that concern was overrated at the time and I think we could  
19 | use the higher dose of Rebetol with the PEG 1.5.

20 |           As in the previous study, the primary endpoint  
21 | for the study, as typical for all chronic hepatitis C  
22 | studies, is the loss of serum HCV RNA 24 weeks post  
23 | treatment.

24 |           In this slide are the demographics for this  
25 | study. These demographics are consistent for studies that

1 have been conducted in Europe and the United States. In  
2 fact, this 1,530 patient study was conducted in 62 centers  
3 in the Americas and Europe. As you can see, they're  
4 balanced across the groups. The patients are predominantly  
5 male. They're predominantly middle-aged and caucasian.

6 I would call your attention to the weight range  
7 in this study. The mean was 82 kilos, and if you remember  
8 our studies from 5 years ago, the weight in the United  
9 States particularly has gone up. In fact, the mean back  
10 then was about 75 kilos. We have a wide range from around  
11 40 kilos to almost 180 kilos. This becomes important later  
12 on.

13 The disease characteristics in these  
14 populations are also well balanced. They are also  
15 consistent with what we've seen in previous studies. The  
16 majority of the patients are genotype 1, high viral load.  
17 So, approximately 70 percent of our patients had HCV-1 with  
18 more than 2 million copies per milliliter.

19 About 30 percent of our patients had evidence  
20 of advanced fibrosis. We used the Knodell HAI and this is  
21 based on F3 and F4.

22 I'd now like to turn to the sustained virologic  
23 response in this study. That was the primary endpoint in  
24 the study. The primary comparison was to be the 1.5 group  
25 versus Intron plus Rebetol.

1           In this study we show the primary endpoint. As  
2 you can see, the basis for this was sustained virologic  
3 response 24 weeks following the end of treatment. This was  
4 calculated using the start date for treatment and going to  
5 24 weeks post treatment. The assessment at 24 weeks post  
6 treatment had to be negative and it had to be within the  
7 28-day window, as specified by the start date of treatment.

8           Using this analysis per protocol, we see that  
9 the response rate in the PEG 1.5 versus Rebetol compared to  
10 the Intron/Rebetol is 52 versus 46 percent with a p of .03.

11           In this population of patients, we had a few  
12 patients who did not meet the window of 28 days for the  
13 follow-up. They were, however, negative. We consider  
14 these patients responders. When you do that and look at  
15 the data, what you see is a 54 percent response rate in the  
16 PEG 1.5/Rebetol versus 47 in the other two treatment  
17 groups. For the subsequent analysis that I will show you,  
18 we will be using this patient population.

19           I'd now like to move to the additional analysis  
20 that we did. Since we had met the primary criteria in the  
21 protocol for efficacy, the 1.5 versus the Intron/Rebetol,  
22 we then proceeded to look at factors that might predict  
23 response. To do this, we used classic techniques. First,  
24 we used univariate analysis by logistic regression, and  
25 what we found is not surprising. It's what you see in all

1 hepatitis studies: genotype non-1, lower baseline viral  
2 load, lighter weight, bridging fibrosis, cirrhosis, age,  
3 and gender to a lesser extent.

4 To determine whether these variables were  
5 independent, we then did multivariate analysis, and what we  
6 found is we retained all of the variables with the  
7 exception of gender. When you account for patient weight,  
8 gender drops out in a multivariate analysis.

9 However, we saw that we still had baseline  
10 weight in this analysis, and we knew from our previous  
11 analysis that we had probably removed as a confounding  
12 factor the PEG dose because we're basing on a weight-based  
13 basis.

14 So, we then proceeded to do some additional  
15 logistic regression, which I will show you, in an attempt  
16 to understand what was influencing our response rate with  
17 weight still there. We decided that we would look at  
18 ribavirin on a milligram per kilogram basis. So, what we  
19 did is we looked at the doses the patients received and  
20 then expressed them as milligram per kilogram.

21 This slide shows the regression analysis that  
22 we did in the PEG 1.5 group, as it is the superior group to  
23 the other three. On the left-hand side, is the percent of  
24 patients who had sustained response when we did this  
25 analysis. Across the x axis, you see the Rebetol expressed

1 as milligrams per kilogram. The dotted line is the fitted  
2 regression line. The circles represent the patient data  
3 expressed as moving averages. The size of the circle  
4 represents the amount of data in that interval. As you can  
5 see, as the dose of ribavirin increases, so does the  
6 sustained response rate.

7 We then wanted to look and see what happened  
8 when you put our Intron/Rebetol data on the same kind of  
9 analysis, and what you see here is the Intron A 3 million  
10 units three times a week with 1,000 to 1,200 milligrams  
11 ribavirin. As you can see from the placement of the  
12 circles -- this is the patient data -- they are further  
13 along the axis on the milligram per kilogram. They  
14 received more ribavirin on a weight basis. As you can see  
15 here, with 800 milligrams of ribavirin and a heavier  
16 patient, they're further down on the axis.

17 We had anticipated that our patients would  
18 weigh about 75 kilos, so we wanted to look and see what an  
19 average 75 kilo person would have received as a dose.  
20 Basically you can see that most of our patients didn't  
21 receive that dose. They received less than 10.6 milligrams  
22 per kilogram. In fact, this is about 60 percent of our  
23 patients and this represents about 40 percent. The  
24 patients in the Intron/Rebetol group, in contrast, received  
25 about 13 milligrams per kilogram, as you can see looking up

1 here.

2           It's difficult to compare data when patients  
3 have received different doses of ribavirin on a milligram  
4 per kilogram basis, so we wanted to look at the observed  
5 response rates, trying to look on a more equal basis the  
6 dose of ribavirin that was received by the patients. So,  
7 what we elected to do is use the break point of a 75 kilo  
8 man, because that's basically what we thought our patients  
9 would weigh, and look at these two groups compared for  
10 observed response rate and look at the response rate in  
11 this group. I will tell you there are very few patients in  
12 this group who received less than or equal to 10.6  
13 milligrams per kilo in the Intron A/Rebetol group. In  
14 fact, there are 22 out of 511.

15           In the next few slides, I'd like to show you  
16 our categorical analysis adjusting for weight on a  
17 milligram per kilogram basis and using that break point of  
18 10.6.

19           This slide is all genotypes. All of the next  
20 slides are set up pretty much the same way. On the y axis,  
21 percent sustained response; in the left-hand columns, the  
22 all-patient dose, Intron A 3 million units three times a  
23 week, 1,000 to 1,200 PEG 1.5, 800 milligrams once daily.  
24 This is the 47 and 54 percent you've seen previously.

25           Then what we did is, controlling for ribavirin

1 use, we used the break point that I described, less than  
2 10.6 milligrams per kilogram, greater than 10.6 milligrams  
3 per kilogram. And when you adjust and try to look on an  
4 approximately equal basis, what you see is the differential  
5 between the Intron A/Rebetol group and the PEG 1.5 group  
6 becomes wider, with a 61 percent sustained response rate in  
7 that group that received PEG 1.5.

8 The next slide shows genotype 1. For the all  
9 patients, what we see is the Intron A/ribavirin group, 33  
10 percent versus 42 percent for the PEG 1.5/800 milligrams.  
11 This is statistically significant at the p .02 level.  
12 Again, when we control for the ribavirin dose and look at  
13 those patients who received at least 10.6 milligrams per  
14 kilogram, we see 34 versus 48 compared to the PEG 1.5  
15 group. These sample sizes are small in these people that  
16 received less in the Intron A group, and I tend to think  
17 that we should not be looking at them as a comparison.

18 The next slide shows the response rate by  
19 genotype 2/3. We have not included 4, 5, and 6 in these  
20 slides because of the small number of patients in our  
21 study.

22 Again, for the all, 79 percent for the Intron  
23 A/ribavirin, 82 percent for the PEG 1.5/800. When we  
24 controlled for the ribavirin dose, you see a differential,  
25 81 to 88 percent. With these drugs, we are seeing very,

1 very high response rates in the 2/3 patients, and we are  
2 very close to properly reaching the maximum when we treat  
3 these patients. These are intent-to-treat analyses  
4 essentially, so we have not accounted for whether the  
5 patient received all their drug.

6 The next slide is fairly complicated, but it's  
7 a set of data that I think people would like to see. It's  
8 set up the same way except it's in table format because of  
9 the complexity of the data.

10 On the left-hand side, what we have done is we  
11 have controlled simultaneously for genotype and viral load.  
12 HCV-1 less than or equal to 2 million/greater than 2  
13 million; HCV-2/3 less than or equal to 2 million, greater  
14 than 2 million. Intron A/Rebetol 1,000 to 1,200; PEG-  
15 Intron 1.5 microgram per kilogram/Rebetol 800; and then the  
16 PEG 1.5 group controlled for ribavirin less than 10.6 and  
17 greater than 10.6 milligrams per kilogram.

18 I'd like to work my way through this slide  
19 because I think there are some interesting things to be  
20 looked at.

21 First, in those patients that we considered to  
22 be low viral load HCV-1, there's a new finding that we  
23 haven't seen with Intron/Rebetol, and that is, when you add  
24 PEG 1.5, the response rate approaches that that we usually  
25 see with genotypes 2/3. Granted, this is a small subset of

1 the population. It's about 20 percent of the HCV-1  
2 patients. So, about 10 percent of the population overall.  
3 But essentially we now have a new group of patients, those  
4 patients who are infected with HCV-1, but in whom we have a  
5 relatively low viral load, we now have a fairly high  
6 response rate compared to the 45 percent in the Intron  
7 A/Rebetol group.

8           There doesn't seem to be much effect of the  
9 ribavirin dose here. I think that this probably needs  
10 further exploration. We had about 100 patients in each  
11 group.

12           I'd like to now turn to the greater than 2  
13 million group, which are the HCV-1 patients that are most  
14 difficult to treat and also the most prevalent. When you  
15 look at the Intron A/Rebetol versus the PEG 1.5/800, the  
16 response rates are essentially the same. However, when you  
17 control for the ribavirin dose, what you do see is you see  
18 a differential that appears in the patients who got the  
19 higher dose of ribavirin.

20           Turning to the HCV-2 and 3 patients, those that  
21 have low viral load and are lucky enough to be both low  
22 viral load and 2/3, have a 91 percent response in the PEG  
23 1.5 dose, as you can see, substantially higher than the  
24 Intron A/ribavirin dose. There's a small differential when  
25 you control for the ribavirin dose, but it's very small.

1           When we look at those patients with more than 2  
2 million copies of virus, it's 77 percent versus 76,  
3 essentially the same, with an incremental benefit when you  
4 control for the ribavirin dose.

5           There's one more slide I'd like to show you. I  
6 keep forgetting that I have this slide. It's a very  
7 interesting slide and we put it in because we hadn't really  
8 look at this data in this particular way before.

9           One of the things that we saw when we looked at  
10 the overall database in the Intron/1,000 to 1,200 versus  
11 the PEG 1.5/800 is that the relapse rate appeared to go up.  
12 This was fairly disturbing because we were hoping that,  
13 indeed, if the relapse rate would stay the same with an  
14 incremental increase in the initial response, we certainly  
15 didn't want it to go up.

16           So, the first question we asked ourselves is  
17 how did dose of ribavirin affect this relapse rate?  
18 Because this is one of the primary characteristics of  
19 ribavirin, that it does affect relapse rate.

20           When we controlled for the ribavirin dose in  
21 the PEG 1.5 group, what we actually see is in those  
22 patients that got less than 10.6, we've got a fairly high  
23 relapse rate. In contrast, when we look at the 1.5 who got  
24 more than 10.6 milligrams per kilogram of ribavirin, we see  
25 very comparable relapse rates and even a bit lower than

1 those in the genotype 1 patients than those we've seen with  
2 Intron A/ribavirin. This says to us that with the addition  
3 ribavirin to PEG, what we're actually seeing is an increase  
4 in the initial response rate with a similar relapse rate  
5 when we add ribavirin to the compound.

6 In summary, PEG-Intron 1.5 micrograms per  
7 kilogram of Rebetol is significantly more effective than  
8 Intron A/Rebetol and PEG 0.5 microgram per kilogram of  
9 Rebetol. The approved regimen is 48 weeks of treatment in  
10 treatment-naive patients. The regimen is PEG 1.5  
11 micrograms per kilogram once weekly plus Rebetol 800  
12 milligrams per day.

13 Further analysis of our database suggests that  
14 weight-based dosing of ribavirin, in combination with the  
15 weight-based dosing that we currently use with PEG, results  
16 in an improved sustained virologic response.

17 The other side of any therapy is safety, and  
18 when we looked at our safety database for these two  
19 compounds, what we saw was the types of side effects  
20 associated with Intron A/Rebetol and PEG-Intron/Rebetol  
21 were very similar. They're the same types. We see no new  
22 side effects. What we did see was an increased incidence  
23 with PEG-Intron/Rebetol. Therefore, we thought it was  
24 important to look at the differences and see where these  
25 increases were occurring, and that is basically the way we

1 | have setup our safety review for you today.

2 |           We've done two things. We've looked at the  
3 | groups of PEG-Intron 1.5/800 versus Intron/Rebetol, and  
4 | then we have also looked at the safety controlling for the  
5 | ribavirin dose as we did in the efficacy.

6 |           The first slide addresses adverse events, and  
7 | what we have elected to do is look at those adverse events  
8 | in which there's a greater than 10 percent difference  
9 | between the treatment groups. The slide is set up as for  
10 | the efficacy slides. Across the top, the Intron/Rebetol  
11 | 1,000 to 1,200 milligrams, the PEG 1.5/800 milligrams, and  
12 | then PEG 1.5 adjusted for milligram per kilograms of  
13 | ribavirin, less than or equal to 10.6, greater than 10.6  
14 | milligrams per kilogram.

15 |           When you categorize adverse events using the  
16 | classic systems, they come out as body systems. What we  
17 | have done here is identified the body system and the  
18 | adverse events under the body system. Application site is  
19 | essentially injection site reaction. And when we look at  
20 | the Intron/Rebetol group versus the PEG 1.5/ribavirin  
21 | group, what we see is an increase in the inflammation, and  
22 | reaction is really nonspecific. That's the fact that the  
23 | patient saw something there. What you will see is there's  
24 | approximately a 1.5-fold increase between the two groups.

25 |           Now, interestingly in this study what we saw

1 was a very high incidence of injection site reaction in the  
2 Intron A/Rebetol group. We think this is because we used a  
3 questionnaire to specifically ask the patient were they  
4 seeing anything at the injection site, and what we got was  
5 an incidence of about twice what we normally see. However,  
6 what we saw in the monotherapy study with PEG versus Intron  
7 was about the same increment of about a 50 percent increase  
8 between PEG and the Intron A. I will tell you that most of  
9 our injection site complaints were mild and there was very  
10 little pain associated with any of these, about 2 to 3  
11 percent.

12 Not unexpectedly, what we call body as a whole,  
13 which is basically flu-like side effects, which includes  
14 fever, rigors, and weight decrease, we saw more than a 10  
15 percent difference in these three side effects when we went  
16 to the higher doses of PEG. This is probably not  
17 surprising, given that 1.5 of PEG-interferon is a lot more  
18 interferon than you're going to get with 3 million units  
19 three times a week.

20 GI side effects. The same situation. There  
21 were more GI side effects with PEG 1.5.

22 And this was an interesting finding that we're  
23 not quite sure what to make of. Alopecia was more frequent  
24 in the high dose Rebetol group when we adjusted for weight  
25 if we looked at PEG 1.5, greater than 10.6 milligrams per

1 kilogram. The only supposition that we have is this group  
2 may have had more women in it, and I can tell you women are  
3 much more sensitive to the alopecia than the men. So, that  
4 may be the reason for that higher incidence. We'll have to  
5 find out in future studies whether indeed this is true.

6 And on the bottom of this we have listed -- and  
7 you have it in your handout -- the incidence of any side  
8 effect that occurred in more than 10 percent of patients in  
9 any treatment group.

10 The outcome of side effects, as far as we're  
11 concerned, are primarily discontinuations and  
12 modifications. These are the important ones that we really  
13 want to look at, and I'd now like to focus on these for a  
14 few minutes.

15 The discontinuations across these treatment  
16 groups, Intron versus PEG 1.5/800 or PEG 1.5 controlled for  
17 the ribavirin dose, are very similar. I would comment, if  
18 you remember the Intron A/Rebetol studies, the dose  
19 discontinuation rates in those studies were about 20  
20 percent. So, we've actually seen the dose discontinuation  
21 rate go down.

22 However, when you look at dose modifications,  
23 there are two things to be looked at. We have about a 34  
24 percent dose modification rate in the Intron A/Rebetol  
25 group. If you look at the PEG 1.5/800, it's 42, and when

1 | we go over here controlling for ribavirin dose, we see it  
2 | goes to 49 percent.

3 |           We think it's very important to take a look and  
4 | understand what those modifications that are causing this  
5 | increased incidence are, and in the next slide what we have  
6 | done is we have looked at reasons for dose modification for  
7 | adverse events that occurred with a greater than 2 percent  
8 | difference between the groups. What we see on the top line  
9 | I think is really the bottom line of why we're seeing dose  
10 | modifications with PEG 1.5, particularly when we weight-  
11 | adjust it for the ribavirin.

12 |           Neutropenia occurred in 8 percent of patients  
13 | in the Intron A/Rebetol group, 18 percent overall in this  
14 | group, and increased slightly when we adjusted for the  
15 | ribavirin dose. The increase in neutropenia is probably  
16 | not surprising. We actually expected it with the PEG 1.5  
17 | dose, and this is what we saw.

18 |           We also looked at anemia, 13 percent in the  
19 | Intron A/Rebetol, slightly lower here, but that is really  
20 | being driven by those patients that got less than 10.6  
21 | milligrams of ribavirin. When you look at those patients  
22 | that got at least the lower limit of the ribavirin dose, in  
23 | these patients it flattens out.

24 |           PEG-Intron monotherapy and alfa-2b interferon  
25 | monotherapy are associated with drops in platelets.

1 | However, when you combine ribavirin with these alpha  
2 | interferons, you get a reactive thrombocytosis that's  
3 | actually due to the hemolysis of the ribavirin. We looked  
4 | at simply the people who had dose modification for  
5 | platelets, 1 percent here, 2 percent here. Interestingly  
6 | more patients received it here probably due to the fact  
7 | they were getting less hemolysis.

8 |           As I mentioned, body as a whole is basically  
9 | flu-like symptoms, malaise, fatigue, and what we see is a  
10 | slight increase over Intron/Rebetol in the PEG 1.5/800,  
11 | whether it's weight-adjusted or not for ribavirin. This  
12 | isn't surprising, again because of the higher dose of PEG.

13 |           GI side effects were slightly higher.

14 |           And I think importantly, a question that  
15 | everybody always asks is what's happening with psychiatric  
16 | events when you use another therapy. What we show here is  
17 | basically in psychiatric events, which are depression, we  
18 | see insomnia. Insomnia, in fact, is a big part of the  
19 | psychiatric events with the alpha interferons. Basically  
20 | the dose modification rates are flat.

21 |           I'd now like to just talk briefly about  
22 | laboratory abnormalities, focusing on the hematologic  
23 | adverse events. I'd like to start with neutrophils. I've  
24 | shown you that we have neutropenia, and I'd like to talk a  
25 | little bit more about what we actually saw.

1                   This slide is set up as the previous slides  
2 with the treatment groups across the top, Intron A, PEG  
3 1.5/800, PEG 1.5 controlled for the ribavirin dose.

4                   In this protocol, patients were required to  
5 come into the study with a minimum of 1,500 neutrophils.  
6 Almost all patients dropped their neutrophil counts, not  
7 surprisingly. We know this happens with alpha interferon.

8                   The protocol required that any patient that had  
9 a neutrophil count that dropped below 750 be dose-modified.  
10 The dose modification was 1.5 for the Intron A and .75 for  
11 the PEG 1.5. Patients who dropped below 500 neutrophils at  
12 any time were to be discontinued from the study. They were  
13 to have both drugs be discontinued and they were not to be  
14 restarted.

15                   What we found was that looking at patients that  
16 had less than 750 neutrophils at any time, that there was  
17 definitely a difference between the Intron A/Rebetol and  
18 the PEG/ribavirin, 18 percent here and a slightly higher  
19 increase in the 1.5 where the ribavirin dose was greater  
20 than 10.6. As you'll notice from the dose modification  
21 slides, these numbers match almost exactly.

22                   There were some patients that had a count of  
23 less than 500, 2 percent here, basically 4 percent here,  
24 and 7 percent over here. However, when you look at those  
25 patients who were discontinued for neutropenia, which they

1 | were to be discontinued at 500, these numbers don't match.

2 |           The reason for that being is we used a central  
3 | lab for this particular study, and sometimes neutrophils  
4 | don't travel well and you'll get back a result that says  
5 | the white count is X and the neutrophil count is below 500.  
6 | We allowed investigators in this study to call the patient  
7 | back in, do a stat WBC, and then make a decision as to  
8 | whether the patient had to be discontinued. And as you can  
9 | see, we do have a discrepancy here.

10 |           Now, when you have neutrophils that drop below  
11 | 500, you always have a concern about infection. What we  
12 | did is we went back in our database and we assured  
13 | ourselves that no patient whose neutrophil dropped below  
14 | 500 had a serious or severe infection. We then looked at  
15 | our serious and severe infections and then determined  
16 | whether any of those patients had a neutrophil count that  
17 | dropped below 750. None of the patients did. So, we  
18 | cannot find a correlation between neutropenia that could be  
19 | associated with infection and severe or serious infection.  
20 | We had no patient die from infection during the study, and  
21 | so we're pretty convinced that the neutropenia we observed  
22 | here is not associated with severe infection.

23 |           I'd like to now take a look at hemoglobin and  
24 | hemolysis. Patients were required to come into the study  
25 | with a hemoglobin of a minimum of 13 grams per deciliter in

1 | males and 12 grams per deciliter in females. The dose  
2 | reduction criteria for this study said that if your  
3 | hemoglobin dropped below 10 grams, that you had to be dose-  
4 | reduced. The reduction was to 600 milligrams per day of  
5 | ribavirin. If your hemoglobin dropped below 8.5, you had  
6 | to be discontinued from the study, and that included  
7 | stopping both drugs. We didn't allow people to stay on  
8 | their interferon if their ribavirin had to be discontinued.

9 |           And what we found was that 12 percent in the  
10 | Intron A/Rebetol group, 9 percent in the PEG 1.5/800, but  
11 | as I showed you previously in the dose modifications, these  
12 | two become very similar when you adjust for the dose of  
13 | ribavirin. Dose reduction was an adequate way of managing  
14 | this toxicity. As you can see, we have very, very few  
15 | patients who discontinued the study for anemia. In fact,  
16 | these are the numbers of patients.

17 |           I would also comment to you that for both  
18 | neutropenia and hemoglobin drops, they are very baseline-  
19 | dependent, and those patients that come in with the minimum  
20 | values often have to be watched. A patient that comes in  
21 | with 12 grams of hemoglobin is more likely to drop to 10  
22 | than the male that comes in with 16.

23 |           In summary, the types of adverse events that we  
24 | observed with Intron and PEG 1.5/Rebetol are similar, but  
25 | there is a higher incidence of some side effects in the PEG

1 1.5/Rebetol group.

2 Neutropenia less than 750 is more frequent with  
3 PEG 1.5/Rebetol than with Intron/Rebetol for both the fixed  
4 dose and the ribavirin adjusted dose.

5 When we look at weight-based dosing with  
6 ribavirin greater than 10.6, we see an increased occurrence  
7 in anemia and neutropenia with those doses.

8 Discontinuations across the group were similar.  
9 They aren't any different. Dose modifications are  
10 certainly more frequent with the PEG 1.5 group and appear  
11 to be really related to the alpha interferon component of  
12 that combination.

13 The incidence of side effects that we see with  
14 the PEG 1.5 either as the 800 or the adjusted for weight-  
15 dosing were adequately controlled with dose modification.

16 Although I didn't mention it, people are always  
17 interested if there are deaths that occur in a clinical  
18 trial. We had two deaths in our trial. One was a motor  
19 cycle accident in the Intron/Rebetol group that we believe  
20 is unrelated to the study. The second one was in the PEG  
21 0.5 group which was a suicide. In our protocol, we  
22 prohibited patients that had ever experienced suicidal  
23 ideation or suicide attempt from entering the protocol.  
24 This patient did not reveal to his physician that he had  
25 previously attempted suicide and committed suicide during

1 the course of the study.

2 As part of the agreement for the approval of  
3 PEG-Intron plus Rebetol, we have agreed with the agency to  
4 conduct certain post-marketing studies. I'd like to now  
5 just briefly describe these.

6 Schering is supporting a study in approximately  
7 4,000 patients. This study is a PEG 1.5 micrograms per  
8 kilogram study once weekly for all patients, combined with  
9 either Rebetol 800 milligrams per day as a flat dose versus  
10 the weight-based dosing of 800 to 1,400 milligrams per day.  
11 So, what we have essentially done is we have tried to  
12 achieve a dose of approximately 13 milligrams per kilogram  
13 plus or minus 2 milligrams per kilogram in all patients.

14 Within this study is a commitment to have at  
15 least 1,000 patients with favorable prognostic factors to  
16 evaluate the effect of duration, 6 versus 12 months.

17 I would also mention that there is a supporting  
18 study going on in Europe with approximately 500 patients.  
19 In this particular study, we're evaluating favorable  
20 prognostic factor patients, genotype 2/3 and HCV-1/low  
21 viral load with treatment for 6 months.

22 The second study that we've agreed to do is a  
23 study in approximately 1,500 patients. This will compare  
24 two doses of PEG-Intron, both compare PEG 1.5 versus PEG  
25 1.0 once weekly administered for 48 weeks. The Rebetol

1 | dose regimen that we will use in this study will be  
2 | determined from study number 1, whether it be 800  
3 | milligrams as a flat dose or a weight-based dosing regimen.

4 |           We have also agreed to evaluate within this  
5 | study at least 100 African Americans for response. I would  
6 | also mention to you that in study number 1, because of the  
7 | large size -- it's probably the largest HCV study that's  
8 | been done to date -- we expect to have about 400 African  
9 | Americans.

10 |           Ribavirin has a food effect. Therefore, we  
11 | have also agreed to further look at this food effect,  
12 | fasted versus low fat versus high fat. Although I didn't  
13 | mention it, because of our knowledge of the food effect,  
14 | the clinical trial with PEG-Intron/Rebetol was done with  
15 | all patients taking their doses with food.

16 |           I'd now like to take the opportunity to  
17 | introduce Dr. John McHutchinson. Dr. McHutchinson is a  
18 | well-known hepatologist and clinical trialist. He's led a  
19 | number of large clinical studies. Dr. McHutchinson, in  
20 | working with me, has been the principal investigator on the  
21 | Intron/Rebetol study that was reported in the New England  
22 | Journal in 1998 and most recently has been co-principal  
23 | investigator on the PEG/Rebetol study that I just reported  
24 | and that was published in the Lancet in September. Dr.  
25 | McHutchinson will now speak briefly about the risk/benefit

1 of treating chronic hepatitis C patients. Dr.  
2 McHutchinson.

3 DR. McHUTCHINSON: Thank you. I appreciate the  
4 opportunity to speak here, on the one hand, as a consultant  
5 but, on the other hand, as a hepatologist trying to care  
6 for many patients with hepatitis C.

7 The decision to treat patients with chronic  
8 hepatitis C involves many factors, and it's a complex  
9 decision making process. While the natural history of the  
10 disease is variable and somewhat controversial, some  
11 patients with chronic hepatitis C do develop progressive  
12 disease and can thus benefit from successful therapy as  
13 judged by viral eradication.

14 Host factors important in this decision making  
15 process include the severity of the disease as established  
16 by liver biopsy and comorbid conditions that, of course,  
17 might prevent a patient from being safely treated with  
18 their current therapies.

19 Likewise viral factors, particularly genotype,  
20 provide a guide to the likelihood of response, and they may  
21 influence the decision to treat. For example, since  
22 patients with genotype 2 or 3 are more likely to respond to  
23 therapy, they may be firstly more willing to undergo  
24 therapy, and their practitioners may be more favorably  
25 inclined to treat them because the likelihood of response

1 | is greater in that group of patients.

2 |           Finally, whilst our current therapies are  
3 | imperfect, the efficacy of therapy, the side effects, and  
4 | the costs also influence this decision making process.

5 |           So, as practitioners treating hepatitis C  
6 | patients, we must weigh the risks of our current therapy,  
7 | their likelihood of success in slightly more than half the  
8 | patients, as you've just heard, the drawbacks and the  
9 | investment of all concerned against the benefits of a  
10 | sustained response. The latter include the normalization  
11 | of ALT values, eradication of serum and liver HCV RNA,  
12 | improvement in liver inflammation, and health related  
13 | quality of life which have been shown to be durable.

14 |           Whilst we have no definitive evidence from  
15 | prospective trials that therapy definitely prevents the  
16 | development of liver cancer or the development of cirrhosis  
17 | or decreases morbidity or mortality or delays the time to  
18 | liver transplantation, we believe there is accumulating  
19 | data to support these longer-term benefits, and we hope  
20 | that in the future, as more data and more outcomes become  
21 | available, we can more firmly establish these goals and  
22 | benefits in due course.

23 |           Now, the decision to treat people with  
24 | hepatitis C also includes two additional factors. First,  
25 | the majority of patients who are acceptable for therapy

1 | have genotype 1 infection and some degree of fibrosis.  
2 | Both are unfavorable factors in terms of their likelihood  
3 | of response. Secondly, treatment involves a significant  
4 | investment in terms of the duration of therapy. The more  
5 | aggressive regimen of the drugs we're using now and the  
6 | time and commitment required by the patient, the  
7 | practitioner, and also the ancillary staff.

8 |           So, how can we achieve the greatest treatment  
9 | benefit whilst diminishing the risks for these patients  
10 | with hepatitis C who are considering therapy or for whom we  
11 | are considering therapy?

12 |           Initially we should provide the best support  
13 | and education available, both before and during a course a  
14 | therapy. Secondly, we should prescribe the most effective  
15 | and safe doses of PEG-Intron and ribavirin. Understanding  
16 | that we will almost universally encounter side effects as  
17 | you've heard, we should monitor these patients closely and  
18 | dose-reduce when necessary rather than discontinuing  
19 | therapy to provide the patient with a continued opportunity  
20 | of responding. And finally, stopping rules allow us to  
21 | discontinue therapy early in those unlikely to achieve a  
22 | sustained response.

23 |           So, taking the data as presented by Dr.  
24 | Albrecht and the issues I've touched on today as a  
25 | practicing hepatologist into account, I believe the

1 risk/benefit ratio for PEG-interferon and ribavirin is  
2 acceptable. While we all realize the need for more  
3 effective and safer therapies in the future, in the  
4 meantime the risks and benefits of our current treatment  
5 with PEG-interferon and ribavirin should be addressed as  
6 part of the individual doctor/patient relationship in an  
7 informed fashion, and the goal should be to provide the  
8 patient with hepatitis C the best chance of a response and  
9 its potential benefits the first time around.

10 Thank you.

11 DR. GULICK: Thanks, Drs. Giles, Albrecht, and  
12 McHutchinson.

13 I'd like to ask the committee if we could hold  
14 questions until after the agency presentation, which will  
15 be next. Dr. Louis Marzella from the agency will give the  
16 next presentation.

17 DR. MARZELLA: I think we're ready to begin. I  
18 apologize for that delay.

19 Mr. Chairman, distinguished members and guests  
20 of the advisory committee, ladies and gentlemen, good  
21 morning.

22 The objectives of the FDA presentations today  
23 are twofold. The first objective is to summarize the  
24 efficacy and safety data which led to the approval of PEG-  
25 interferon and ribavirin for the treatment of adults with

1 | chronic hepatitis C. The second objective of our  
2 | presentation is to discuss the outstanding issues which  
3 | remained at the time of the approval which led to the FDA  
4 | request for additional postmarketing studies.

5 |           In our presentation, we will focus on what in  
6 | our view are the main issues, namely the need for further  
7 | dose optimization of PEG-interferon and ribavirin.

8 |           We will begin by reviewing the design of the  
9 | phase III study and discuss the rationale for the selection  
10 | of the PEG-interferon and ribavirin doses which were used  
11 | in the phase III study. For the purpose of dose selection,  
12 | in-treatment data from PEG-interferon monotherapy trials  
13 | and small dose-ranging trials of interferon and ribavirin  
14 | were used. As I will discuss, the dose in-treatment data  
15 | turned out to be not very predictive.

16 |           We will then consider the summary of efficacy,  
17 | and we will begin by considering the prespecified analysis  
18 | focusing on the primary efficacy outcome, and we will then  
19 | discuss the efficacy data in specific patient subsets  
20 | focusing on weight-adjusted ribavirin dosage.

21 |           We will then briefly consider the safety  
22 | profile of PEG-interferon and ribavirin and compare it to  
23 | that of interferon/ribavirin. Again, we will review  
24 | subgroup analysis to look at the effects of weight-adjusted  
25 | ribavirin dosage on safety.

1           We will conclude then with a summary of the  
2 postmarketing commitments. As you've heard already,  
3 Schering committed to carrying out further studies to  
4 optimize the dosage of PEG-interferon and ribavirin, to  
5 define the optimal duration of treatment in patient  
6 subgroups, and of particular interest here are patients  
7 that have baseline characteristics which predict good  
8 response to treatment. Safety and efficacy  
9 characterization in African Americans is necessary because  
10 historically this patient population is known to not  
11 respond as well as other ethnic groups to treatment. And  
12 finally, Schering committed to further characterizing the  
13 effect of food on ribavirin absorption.

14           Let's begin by looking at the design of the  
15 phase III combination study. This was a 1,500 patient  
16 study. The design was multicenter, randomized, open-label.  
17 The active control was interferon and ribavirin in patients  
18 who are treated for 48 weeks and followed up for 24 weeks.  
19 The primary outcome measure, the loss of HCV RNA detection,  
20 was determined at 24 weeks of follow-up.

21           As you heard before, the three arms in the  
22 study were an arm in which a high dose of PEG-interferon  
23 was used. This was 1.5 micrograms per kilogram weekly. In  
24 this arm, patients received a flat dose of ribavirin,  
25 namely 800 milligrams per day.

1                   In the low PEG-interferon arm, patients  
2 received 0.5 microgram per kilogram weekly, and ribavirin  
3 was given as either 1,000 or 1,200 milligrams per day. In  
4 other words, there was a crude dose adjustment for  
5 ribavirin, and note that the ribavirin dosage was higher in  
6 this arm. Of note is also the fact that in this arm  
7 patients received a 1-month induction treatment with high  
8 dose PEG-interferon.

9                   Then finally, the standard treatment arm at  
10 that point for this particular trial was interferon 3 times  
11 10 to the 6th million units three times weekly and  
12 ribavirin, again the "high dose" with crude dose adjustment  
13 based on body weight with patients receiving either 1,000  
14 or 1,200 milligrams per day.

15                   The most significant protocol amendment after  
16 the study began was a provision that patients take  
17 ribavirin with food, and the reason for this amendment was  
18 that data from a clinical study became available which  
19 indicated that food had a major effect on absorption of  
20 ribavirin, increasing the absorption as much as 70 percent  
21 in the presence of food compared to the fasting state.

22                   Now, let's focus on the rationale for the  
23 selection of the PEG-interferon dosage. Let me clarify one  
24 point. The phase III combination study refers to the PEG-  
25 interferon/ribavirin study. This needs to be

1 differentiated from the PEG-interferon monotherapy study  
2 which was performed earlier and led to the approval of PEG-  
3 interferon for monotherapy of chronic hepatitis C.

4 Now, this slide shows the treatment response at  
5 the end of 6 months of treatment, as well as at the end of  
6 the 6 months' follow-up at the end of the 1 year of  
7 treatment. As you can see, the in-treatment response  
8 tended to show a dose response in the range of between 0.5  
9 and 1.5 micrograms per kilogram. This in-treatment data  
10 suggested that the high-dose PEG-interferon might be the  
11 most efficacious. And on the basis of this, therefore, the  
12 sponsor selected the 1.5 microgram per kilogram dose to  
13 study in the phase III study.

14 Now, unfortunately, at the completion of the  
15 PEG-interferon monotherapy study, data showed that whereas  
16 PEG 1.5 was superior to interferon, it was not actually  
17 superior to PEG 1 microgram per kilogram. And in addition,  
18 the high PEG-interferon dose showed an increased toxicity.  
19 For these reasons, the agency licensed then, because of the  
20 demonstrated efficacy, PEG-interferon monotherapy for the  
21 treatment of adults with chronic hepatitis C, and the  
22 agency recommended a dose of PEG-interferon of 1 microgram  
23 per kilogram.

24 Now, while these data were under review, the  
25 combination phase III study was already completed. For

1 | this reason then, the PEG 1 microgram per kilogram dose was  
2 | never studied and no data about safety and efficacy of this  
3 | dose was available for this review.

4 |           Now, let's consider the rationale for the  
5 | selection of the ribavirin dosage for the phase III  
6 | combination study. This selection was primarily based on a  
7 | small dose-ranging study which included about 70 patients,  
8 | and in this study the following range of PEG-interferon  
9 | doses were used, between 0.35 and 1.4.

10 |           In addition, patients received a range of  
11 | ribavirin dosages. I will not show the data because the  
12 | numbers are so few. Suffice it to say that the results  
13 | suggested that low doses of PEG-interferon tended to work  
14 | only with higher ribavirin dosages; whereas in the arm  
15 | where patients received 1.4 micrograms per kilogram, as low  
16 | as a 600 milligram dose, flat dose, of ribavirin turned out  
17 | to show evidence of virologic activity. For this reason  
18 | then, the sponsor chose the 800 milligram flat dose hoping,  
19 | in so doing, to minimize toxicity due to ribavirin without  
20 | compromising efficacy. These data that led to the  
21 | selection of the ribavirin dose were also based on in-  
22 | treatment responses.

23 |           Now, let me focus then on the primary efficacy  
24 | outcome of the trials, sustained virologic response. This  
25 | was defined as loss of detection of HCV RNA 24 weeks after

1 the end of treatment. The prespecified efficacy analysis  
2 stated that the high-dose PEG-interferon arm was to be  
3 compared to the interferon/ribavirin arm.

4 There were two stratification variables in this  
5 study. One was the presence of viral genotype 1 at  
6 baseline and patients were dichotomized into either  
7 genotype 1 versus non-1, and the other stratification  
8 factor was the presence of liver fibrosis. These  
9 stratification variables were then also used in a  
10 prespecified fashion in the efficacy analysis. The data  
11 was adjusted for these factors.

12 The initial study design foresaw an equivalency  
13 comparison and a non-inferiority margin was selected and  
14 prespecified, and it was designed to exclude an  
15 unacceptable loss of efficacy of the new treatment compared  
16 to the old treatment.

17 As you can see here, the proportion of  
18 responders in the PEG 1.5/ribavirin arm was 52 percent  
19 compared to 46 percent in the interferon/ribavirin arm.  
20 So, the treatment difference was 6 percent. It was modest.  
21 The PEG 0.5/ribavirin arm was not superior to the  
22 interferon/ribavirin arm.

23 Now, let me then move on and consider treatment  
24 outcomes based on patient subsets. Let me clarify again  
25 that the prespecified subgroup analyses were, as I

1 indicated, presence of viral genotype 1 and presence of  
2 cirrhosis. Post hoc analyses were based on viral titers,  
3 age, gender, and ethnicity, geographic location, and body  
4 weight.

5 Now, let me, in passing, cite the effects of  
6 age, gender, and ethnicity on the treatment outcome because  
7 I will not dwell on those. There was a correlation between  
8 a younger age and a higher treatment response. There was  
9 also an effect of gender on treatment response with women  
10 having apparently a higher treatment response. Treatment  
11 responses also tended to be lower, as it's known, in  
12 African Americans.

13 Now, let's consider the effect of baseline  
14 viral genotype on treatment response. In this particular  
15 slide, what we have done is looked at patients with  
16 genotype 1, subdivided in patients that had high viral  
17 titers at baseline or low viral titers. High viral titers  
18 is defined as greater than 2 million particles of HCV RNA  
19 per ml of serum.

20 As one can see here, the responses tended to be  
21 greater in patients with low viral titers. Looking at a  
22 comparison between interferon/ribavirin and PEG 1.5, there  
23 appears to be a higher response to treatment in patients  
24 who have genotype 1 and low viral titers.

25 Now, it's somewhat not clear whether or not

1 | this indicates that patients with specific prognostic  
2 | factors are more likely or less likely to have superior  
3 | responses to PEG-interferon compared to interferon. As you  
4 | can see, the patients with genotype 1 and high viral  
5 | titers, who were the patients who have the worst prognostic  
6 | outlook, really essentially have similar response rates to  
7 | PEG-interferon/ribavirin and interferon/ribavirin.

8 |           Now, let's also look at treatment response in  
9 | patients with other genotypes, genotypes 2 to 6. Again,  
10 | this slide subsets these patients based on viral titers at  
11 | baseline. As one can see here, there's essentially no  
12 | suggestion of difference between interferon/ribavirin and  
13 | PEG 1.5/ribavirin based on these prognostic indicators.  
14 | So, if one looks at the patients with the better prognostic  
15 | factors, there's no clear indication that PEG-interferon is  
16 | likely to result in higher response rates. If one looks,  
17 | as we did in the previous slide, at patients with the worst  
18 | possible prognostic outcome, again there's no difference.  
19 | So, it's not clear with what assurance to look at the data  
20 | that shows that the patients with genotype 1 and low viral  
21 | titers have apparently superior response rates.

22 |           Now, let's consider treatment response by  
23 | geographic location. For the purpose of this analysis, the  
24 | patients are divided in patients seen in U.S. centers and  
25 | non-U.S. center. Non-U.S. centers were primarily centers

1 in Europe, as well as a few centers in Canada and  
2 Argentina. The general considerations are that patients in  
3 U.S. centers tended to have lower response rates than  
4 patients in non-U.S. centers. The reasons for this might  
5 be related to the fact that prognostic factors were less  
6 favorable in patients in the U.S., things such as incidence  
7 of viral genotype 1 tended to be higher, incidence of high  
8 viral titers tended to be high, and interestingly also,  
9 body weight, which was a factor in the treatment response,  
10 was also considerably higher in patients in the U.S.

11 Another comparison of interest is that in  
12 comparing across treatment arms in the U.S., the overall  
13 difference in treatment response indicating a superiority  
14 for PEG 1.5/ribavirin seems to be supported.

15 Now, let me then turn to another major issue  
16 which is the issue of performing efficacy and safety data  
17 based on weight-adjusted ribavirin dosage. The sponsor in  
18 the presentation I think has done a very good and balanced  
19 job of presenting the data based on regression analysis, as  
20 well as analysis based on categorical cuts of the data.  
21 However, we feel that caution is called for in interpreting  
22 the results of these analyses.

23 The first point is that these analyses are post  
24 hoc and were not prespecified.

25 The next point to consider is that the true

1 variable being considered in these analyses is really body  
2 weight, and that the hypothesis being considered is that  
3 body weight is in fact a surrogate for ribavirin dosage.

4 Now, there were substantial differences in  
5 dosages across study arms, and we think that this is a  
6 fundamental problem which makes it very difficult, if not  
7 impossible, to compare treatment response across arms.  
8 This slide essentially compares the PEG or interferon  
9 dosage across treatment arms, and it shows that the PEG-  
10 interferon dosage was weight-adjusted in the PEG-interferon  
11 arms but was not weight-adjusted in the interferon arm.  
12 Ribavirin dosage was lower in the PEG 1.5 arm, and there  
13 was no weight adjustment for the dosage. The ribavirin  
14 dosage, however, was higher in the PEG 0.5 and interferon  
15 arms, and a crude adjustment based on weight was performed.

16 So, for this reason then, these analyses are  
17 essentially based on nonrandomized subgroups that differ,  
18 as I will show you in a minute, very substantially in terms  
19 of numbers body weight, and may well differ in other  
20 unknown factors. However, as I will show later, within-arm  
21 comparison is suggestive. It indicates that weight is  
22 certainly a factor predictive of response, but the data are  
23 too few and inconsistent. Again, the basic point is that  
24 across-arm comparisons are not appropriate in our view.

25 These are the data showing treatment response

1 by ribavirin dosage. In this particular slide, the  
2 ribavirin dosage is divided in dose quartiles. The  
3 numerator shows the numbers of patients responding in that  
4 particular subset, and the denominator is the overall  
5 number of patients.

6 I think that the point that I want to emphasize  
7 is that there is a rather large difference in the number of  
8 patients within each subset. There tended to be very many  
9 more patients in these two arms in this subset, in this  
10 higher exposure subset. Essentially a lot of the data for  
11 the 1.5 came really from patients who received relatively  
12 lower doses of ribavirin.

13 So, the point to emphasize is that there's  
14 extremely limited data upon which to really base an  
15 analysis of safety and efficacy of higher doses of  
16 ribavirin in the licensed PEG 1.5 interferon group. As you  
17 can see then, the median dosage was quite different between  
18 the groups, as well as there was a large range of  
19 differences within arms.

20 So, let's then look at, in fact, adjusting for  
21 weight for ribavirin, what the treatment outcome was. We  
22 did a number of analyses, and the analyses of subgroups  
23 were not really consistent, particularly looking at  
24 patients in the U.S. The reasons can be multiple. There  
25 are differences in prognostic factors, differences in body

1 weight. There is apparently no evidence of interactions,  
2 for instance, in the low PEG 0.5 arm. So, there are trends  
3 basically but the trends are very difficult to interpret.

4 If one looks, however, at dichotomized groups  
5 based on body weight, we feel that the important point to  
6 emphasize is that whether you look at the low body weight  
7 patients or higher body weight patients, that the relative  
8 difference between arms is essentially the same.

9 Now, I also need to briefly mention at least  
10 the population PK and PD study which was done as part of  
11 the pivotal trial. Serum samples were obtained and  
12 analyzed for ribavirin dosage, and modeling was done to  
13 look at clearance of the drug, as well as analyzed  
14 virologic response and safety. For the purposes of safety,  
15 anemia was the only parameter looked at.

16 There were some shortcomings to these analyses.  
17 There are some remaining issues which are still being  
18 discussed between the agency and the sponsor. The main  
19 issues are that basically the simulation of safety and  
20 efficacy did not follow the proposed dosing that the  
21 sponsor proposed, ribavirin dosing. There was little or no  
22 data for patients at the higher exposures, and then there  
23 were issues related to whether ideal body weight should be  
24 used in the analysis, as well as pooling the data and not  
25 performing the analysis based on separating out subgroups

1 | by gender.

2 |           Let me move next to a consideration of the  
3 | safety data, and I will be very brief here and focus  
4 | primarily on the comparison between the high dose PEG-  
5 | interferon and ribavirin arm and interferon and ribavirin  
6 | group.

7 |           I think the basic message here is that  
8 | PEG/ribavirin compared to interferon/ribavirin is  
9 | associated with a higher incidence of toxicities. I think  
10 | it's particularly noteworthy to look at the number of dose  
11 | modifications. In the clinical trial, there were very  
12 | strict entry rules which excluded patients who would have a  
13 | high likelihood of having adverse reactions. There were  
14 | also very specific dose-modification rules which governed  
15 | dose reductions, as well dose discontinuations for patients  
16 | who experienced toxicities. And of course, monitoring was  
17 | very intensive as appropriate in an efficacy trial.

18 |           Particularly as related to the issue of the  
19 | unproven hypothesis that higher ribavirin doses might  
20 | increase response rates, concerns we would have would be  
21 | that these increased dose modifications might be associated  
22 | in actual medical usage with increased toxicity because  
23 | it's common experience that follow-up and dose modification  
24 | might not be as tight outside of clinical trials.

25 |           There were a number of serious and severe

1 | adverse events which were greater in the PEG/ribavirin arm  
2 | compared to the interferon/ribavirin. A particular concern  
3 | here is the suggestion of a synergistic effect between PEG-  
4 | interferon and ribavirin on bone marrow toxicity. So, of  
5 | particular interest are the issues related to neutropenias  
6 | and of infections.

7 |           Then looking at overall adverse events of all  
8 | severities, as the sponsor has previously suggested, there  
9 | was a tendency for specific adverse events to have a higher  
10 | incidence of occurrence.

11 |           Now, let me then focus on the subset analysis  
12 | based on ribavirin weight-adjusted dose and focus again on  
13 | these issues, dose reduction and adverse events. I would  
14 | like to throw out for your consideration the possibility  
15 | that there might be actually a suggestion of a threshold  
16 | where the increase in ribavirin toxicity may be steeper,  
17 | but these are just suggestions.

18 |           Focusing then on serious infectious adverse  
19 | events, these are listed by the classic clinical trial mode  
20 | of -- I'm blocking now the classification. I think the  
21 | point that is important to make is that there's a  
22 | suggestion here of a dose response in terms of the  
23 | incidence of serious infectious adverse events.

24 |           Now, as the sponsor discussed in their  
25 | presentation, there's no evidence in the trial of an

1 association between serious infectious adverse events and  
2 actual decrease in neutrophils, but obviously this is not  
3 cause for reassurance. In looking at the overall safety  
4 database, we have seen this as a concern, this incidence of  
5 serious infections, including lethality, in interferon  
6 products.

7 Now, let's look at the issue of dose  
8 modification in patient subsets defined by body weight, and  
9 let's focus on the PEG 1.5/ribavirin arm. These are the  
10 body weight categories. Again, this is the variable that  
11 we're looking at. This variable translates in these ranges  
12 of ribavirin dosages. As you can see here, there's a  
13 tendency for dose reductions to increase.

14 I should also caution you that numbers are  
15 progressively fewer as we go towards lower body weight.  
16 So, one has to take it with a grain of salt the actual  
17 incidences in these groups. But again, there's a tendency  
18 for not only classic ribavirin toxicity such as anemia to  
19 increase in patients with lower body weight compared to  
20 patients with higher body weights, but also things like  
21 neutropenia show a tendency to increase.

22 I'm sorry. I misspoke. This actually doesn't  
23 look at incidence of adverse events. This looks at  
24 modification of dose.

25 Now, this slide actually then compares the

1 actual incidence of anemia and neutropenia. Again, the  
2 same trends can be seen here. Patients with lower body  
3 weight appear to have a higher incidence of anemia compared  
4 to patients with higher body weight. In the severe to  
5 life-threatening category, there also seems to be a general  
6 trend. So, this reflects then potentially increases in  
7 toxicity due to at least anemia and neutropenia with  
8 potentially higher exposure to ribavirin.

9 To conclude then, the review of the data showed  
10 that PEG-interferon and ribavirin, the 1.5 microgram per  
11 kilogram plus 800 milligram ribavirin, dose is more  
12 effective than interferon plus ribavirin for inducing  
13 sustained HCV response.

14 I didn't discuss the data but most responders,  
15 about 95 percent, to PEG-interferon/ribavirin do so by week  
16 12.

17 Sustained response rates are higher in  
18 genotypes 2 and 3 and lower with genotype 1. Patients with  
19 genotype 1 and high viral loads have the poorest response  
20 of all.

21 As I indicated earlier, in our view there's no  
22 clear indication that particular subsets of patients based  
23 on prognostic factors are more or less likely to have  
24 higher responses with PEG-interferon/ribavirin compared to  
25 interferon/ribavirin.

1 PEG-interferon plus ribavirin is associated  
2 with a higher number of adverse events, for example,  
3 infections, neutropenia, and injection site reactions,  
4 compared to interferon/ribavirin.

5 Few safety or efficacy data exist for African  
6 Americans, a group with a high incidence of HCV hepatitis  
7 and a group known to have a poor response to interferon.

8 Compared to patients with higher body weights,  
9 patients with lower body weights tended to have higher  
10 response rates and higher rates of toxicity. However, as I  
11 indicated, a number of factors could account for this  
12 apparent effect of body weight on treatment response and  
13 toxicity and due to the study design, analysis of these  
14 subsets are particularly troublesome. So, for this reason  
15 definite conclusions about the safety and efficacy of PEG-  
16 interferon plus ribavirin as a weight-based regimen cannot  
17 be drawn based on these data.

18 This then leads me to conclude by then  
19 describing the postmarketing studies that are designed to  
20 assess the safety and efficacy of PEG-interferon plus  
21 ribavirin as a weight-based regimen and the safety and  
22 efficacy of shorter durations of PEG-interferon plus  
23 ribavirin in patients with high likelihood of response.

24 Now, for the members of the advisory committee,  
25 in your briefing package -- as well as for the public,

1 | posted on the web -- are the studies that the agency and  
2 | the sponsor agreed to, but the actual design of the studies  
3 | is in evolution for reasons of increasing the efficiency of  
4 | the studies. For instance, these two aims were combined in  
5 | a large trial, which is a multicenter, randomized, open-  
6 | label trial in approximately 4,000 treatment-naive patients  
7 | with chronic hepatitis C.

8 |           In this particular study, there are two main  
9 | arms. One arm will receive a fixed dose of ribavirin. The  
10 | other arm will receive weight-adjusted ribavirin. Within  
11 | each study arm, then the other variable to be looked at is  
12 | the duration of treatment. So, in arm A, patients will  
13 | receive 1.5 micrograms per kilogram of PEG-interferon plus  
14 | ribavirin 800 milligrams as a flat dose for either 24 weeks  
15 | or 48 weeks. In arm B, the patients will receive 1.5  
16 | micrograms per kilogram of PEG-interferon and ribavirin  
17 | roughly dose-adjusted to provide around 13 milligrams per  
18 | kilogram daily, again for either 24 or 48 weeks.

19 |           And the two lines below show essentially the  
20 | groups. Patients with less than 65 kilograms would receive  
21 | 800 milligrams. Patients in this weight range would  
22 | receive 1,000; this dose range, 1,200; and then patients  
23 | with body weight greater than 105 would receive 1,400  
24 | milligrams of ribavirin per day.

25 |           Then in the next study, two objectives were

1 pooled together, and this particular study then will look  
2 further at the issue of dose optimization of PEG-interferon  
3 by comparing the 1.5 micrograms per kilogram dose to the 1  
4 microgram per kilogram dose. In this study, approximately  
5 1,000 patients with chronic hepatitis C of genotype 1 will  
6 be studied.

7 As the sponsor indicated, the dose regimen of  
8 ribavirin will be determined from in-treatment data in the  
9 ongoing ribavirin dose optimization study.

10 Then the final objective of the study is also  
11 to assess safety and efficacy of the treatment in African  
12 Americans.

13 Now, this slide compares the response to  
14 treatment at the end of 6 months of treatment, as well as  
15 at the end of 6 months of follow-up in the three treatment  
16 arms. This is data from the phase III study. Essentially  
17 what this data indicates is that the in-treatment responses  
18 at week 24 tend to be predictive of the sustained viral  
19 responses essentially in all the dose groups, indicating  
20 that, for instance, the PEG 1.5 arm is the highest apparent  
21 response rate. Again, this leads us to use the in-  
22 treatment data from the ongoing study to decide which  
23 ribavirin dose regimen to use in the PEG-interferon  
24 optimization study.

25 This is my final slide. Finally, the final

1 | commitment is to look at the relative bioavailability of  
2 | ribavirin compared to the fasted state after a high fat  
3 | meal and non-fat meal.

4 | Thank you.

5 | DR. GULICK: Thanks, Dr. Marzella.

6 | We now have an opportunity for the committee  
7 | members to pose questions either to the sponsor or to the  
8 | agency. Dr. Mathews will start us off.

9 | DR. MATHEWS: I have a couple of questions for  
10 | the sponsor. The first one relates to any analyses that  
11 | you've done that showed -- I suppose more of an on-  
12 | treatment analysis -- whether there was a decrement in  
13 | response rates in patients who had to be dose-reduced for  
14 | ribavirin and/or interferon during treatment.

15 | And the second question relates to  
16 | constitutional symptomatic toxicity. I believe what you  
17 | showed us was the proportion who had flu-like illness,  
18 | myalgias, and so on, but did you do any analyses on number  
19 | of treatment days that were symptomatic or severity of  
20 | symptoms when you compare the dosing with the longer-acting  
21 | preparation to the three times a week?

22 | DR. ALBRECHT: Let me address the first  
23 | question that you had with regard to the effect of dose  
24 | reduction. One of the analyses that we've done, and in  
25 | fact has been submitted for publication, is an analysis

1 that looks at the ability of the patient to take his  
2 medication. We call this the 80-80-80 analysis.  
3 Essentially what it says is the patient was able to receive  
4 at least 80 percent of his prescribed drug without dose  
5 modification for 80 percent of the duration. What we see  
6 is that in those patients, the response rates are higher.

7 It's very difficult to look back and look at  
8 the effect of the two different drugs individually and what  
9 dose reduction to the patient does.

10 I think it's important to mention that with the  
11 1.5 dose, we're reducing those patients to .75, and if you  
12 looked at the response rate with the PEG .5, it's very  
13 similar to the Intron A/Rebetol. So, you're basically  
14 sitting with a patient on a PEG dose that is probably still  
15 effective. What we do see is when we reduce the ribavirin  
16 dose to 600, we do see a decrement in response rate.

17 You asked if we looked at number of days of  
18 symptomatology with regard to side effects with the longer-  
19 acting preparation versus the shorter-acting preparation.  
20 No, actually we didn't look at the data that way.

21 DR. MATHEWS: Maybe Dr. McHutchinson could  
22 comment based on your experience. If you treat them once a  
23 week is the duration of the symptoms throughout the dosing  
24 interval or just in the beginning?

25 DR. MCHUTCHINSON: My observations might not be

1 representative of the whole study, of course, but with that  
2 caveat, I think the most information that's come in respect  
3 to whether the long-acting, once-a-week interferon is more  
4 difficult for the patients in terms of symptoms is to look  
5 at people who've been involved in this trial and  
6 particularly in other previous treatment trials where  
7 they've already been exposed to three-times-a-week  
8 interferon and now they've been subsequently treated with  
9 once-a-week interferon.

10 To summarize, I think there are two groups of  
11 patients. There's a group of patients who prefer the once-  
12 a-week interferon. It sort of smooths out the side effect  
13 profile over the week. They're not getting that hectic  
14 fever after the night following the three-times-a-week  
15 injection. And there's a group of patients that seem to  
16 feel worse on the PEG-interferon.

17 So, I mean, I cannot say it's 50/50. I  
18 specifically ask them about this because it's of interest  
19 to us. Many of the patients feel it's smoother with the  
20 PEG-interferon, and some of them don't. They don't fare as  
21 well. That would be my answer.

22 DR. GULICK: Dr. Schapiro?

23 DR. SCHAPIRO: Along those lines --

24 DR. MCHUTCHINSON: I'm sorry. And whether it's  
25 dose-related in terms of low dose/high dose PEG, I think it

1 | is obviously dose-related. The side effects are less in  
2 | the lower doses of PEG-interferon than they are with the  
3 | high doses. That's my clinical observation as you asked.

4 | DR. SCHAPIRO: Along those lines, were formal  
5 | quality of life assessments done? Is there data to  
6 | actually look at the quality of life of the different  
7 | regimens?

8 | DR. ALBRECHT: As published, for the other  
9 | studies, we used the same quality of life instrument, the  
10 | SF-36, in these patients. Surprisingly, when these  
11 | patients are on therapy, their quality of life gets worse,  
12 | and it happens whether you use Intron plus ribavirin,  
13 | whether you use Intron alone, whether you use PEG. So,  
14 | there is a decrement in their quality of life.

15 | The only thing that we can show is in a subset  
16 | analysis which people basically do not agree with, and that  
17 | is, if you look at the baseline quality of life in the  
18 | patients who become sustained responders and then look at  
19 | their quality of life after they've been off the drug for 6  
20 | months, these patients in general are doing better. But  
21 | that's probably related to their sustained response. So, I  
22 | think quality of life with these kinds of drugs are very  
23 | difficult because, obviously, there's a very big decrement  
24 | in quality of life during treatment.

25 | DR. SCHAPIRO: So, you didn't detect a

1 difference between the arms.

2 DR. ALBRECHT: We did not detect a difference  
3 between the arms in this study.

4 DR. SCHAPIRO: The other question was on  
5 autoimmune side effects. I don't think we saw the data.  
6 Most of these side effects seemed to be reversible when  
7 drug was stopped. Sometimes with autoimmune disorders,  
8 that can be an issue. I didn't see any of the data on the  
9 autoimmune disorders, and to what degree they were in the  
10 different arms.

11 DR. ALBRECHT: As you see with alpha  
12 interferons, we did have patients who developed thyroid  
13 dysfunction during the course of the study. Some of these  
14 patients were treated successfully and stayed on their  
15 drug, having their thyroid dysfunction treated. In  
16 general, when you look at the database, when these patients  
17 come off drug, they return to baseline.

18 Other autoimmune disorders we didn't see -- Dr.  
19 Cohard? No. We didn't see. We looked in the database  
20 very clearly. We don't see any difference in other  
21 autoimmune disorders.

22 I will say, however, the protocol clearly  
23 excludes those patients that have autoimmune disorders from  
24 coming into the trial. In fact, it's excluded in our label  
25 for both of the alpha interferons.

1 DR. SCHAPIRO: So, you didn't see irreversible  
2 autoimmune disorders.

3 DR. ALBRECHT: That's correct. Dr. Cohard,  
4 yes? That's correct.

5 DR. MARZELLA: To be more precise, even after  
6 the treatment is discontinued, some of these events do  
7 continue, for instance, the thyroiditis. Others, for  
8 instance, colitis, resolved promptly upon discontinuation  
9 of treatment. So, it's a mixed picture. But  
10 discontinuation of treatment does not necessarily lead to  
11 resolution of the autoimmune phenomenon at least during the  
12 observation period which is 6 months following the end of  
13 treatment.

14 DR. GULICK: Dr. Kumar.

15 DR. KUMAR: I would like to specifically ask  
16 regarding new psychiatric issues that occurred during the  
17 follow-up phase of the study. Page 21 of the briefing  
18 material that was given to us said that some patients  
19 experienced ongoing or new serious adverse events during  
20 the 6-month follow-up period. 13 patients experienced  
21 life-threatening psychiatric events, including suicidal  
22 ideation or attempt.

23 My questions to you are you specifically  
24 excluded patients that physicians knew had underlying  
25 psychiatric illness before entry. So, were there any other

1 risk factors that predisposed these patients? And why do  
2 you think that even after the treatment was completed  
3 during the 6 months of follow-up, that they were at  
4 increased risk?

5 DR. GULICK: Just to clarify, that's page 21 in  
6 the FDA briefing document.

7 DR. MARZELLA: Just to comment, I think that  
8 there was a progressive increase in incidence of  
9 psychiatric adverse events. It did decrease following the  
10 discontinuation of treatment, but it was still higher  
11 compared to baseline.

12 DR. KUMAR: No. My questions are again for  
13 clarification in my own mind. After you stopped the  
14 treatment, did you still see psychiatric events, and if so,  
15 how do we explain that? And were there risk factors that  
16 predicted who would have new suicidal ideations once you  
17 stopped treatment?

18 DR. SIEGEL: I would note, over the years for a  
19 variety of interferon products, we have consistently  
20 observed reports of new suicides or suicide attempts or  
21 ideation occurring in the several months following  
22 treatment. It's not easy to know the association or the  
23 reason, but I think we would expect that it's a real  
24 phenomenon, that it is treatment related based on the  
25 numbers we've seen and the screening going into the trial.

1                   Going back to my medical school days -- and  
2 this is highly speculative, but it's been suggested that  
3 there's often a higher risk of suicidal attempts as people  
4 are coming out of depression as they have more wherewithal  
5 to consider actually doing things than in depression.  
6 Again, that would be speculative. And I think any other  
7 response as to why we see that in the months following  
8 treatment would also be equally speculative.

9                   We are inclined to believe it's real. It's not  
10 specific for this product. It's not particularly higher  
11 post treatment than during treatment, but it appears to be  
12 higher than one would expect to be occurring had there not  
13 been treatment.

14                   DR. KUMAR: May I ask a follow-up question?

15                   DR. GULICK: Sure.

16                   DR. KUMAR: Was this higher in patients that  
17 received the higher doses of interferon? Was there a dose  
18 relation?

19                   DR. MARZELLA: No.

20                   DR. KUMAR: Thank you.

21                   DR. GULICK: Did the sponsor wish to comment  
22 further?

23                   DR. ALBRECHT: No.

24                   DR. GULICK: Dr. Wood.

25                   DR. WOOD: My first question is for the study

1 sponsor regarding dose modification. There is, from the  
2 FDA data, a lower incidence of neutropenia, but we didn't  
3 get the breakout in terms of whether or not there was less  
4 dose modification for the dose intensification arm where  
5 they got 1.5 for 4 weeks and then 0.5 thereafter. So,  
6 that's the first question, whether or not there was less  
7 dose modification for any reason, either neutropenia or  
8 anemia.

9 The second --

10 DR. GULICK: Do you want to tackle one at a  
11 time?

12 DR. WOOD: Okay. We'll tackle one at a time.

13 DR. ALBRECHT: Dr. McHutchinson can also  
14 address this in that we worked on the data together quite  
15 extensively, if you'd like to.

16 In the group to which you refer, there was an  
17 induction arm, the 1.5 for 4 weeks. Dose modification in  
18 that arm was very, very high. Patients didn't like that  
19 high dose, it seemed, in that arm. So, you have to  
20 separate out the dose modification, the first 4 weeks  
21 versus the next 44 weeks. If you look at the first 4  
22 weeks, it's equivalent to the 1.5 arm that received 48  
23 weeks of the 1.5. So, the dose modifications look similar.  
24 If you look at the next 44 weeks, the incidence of dose  
25 modification looks similar to that seen with

1 | Intron/Rebetol. In fact, .5 and Intron/Rebetol looked  
2 | very, very much alike. So, when you think about that  
3 | particular arm, you have to think about the first 4 weeks  
4 | and what happened with dose modification versus the next 44  
5 | weeks, and the next 44 weeks looks similar to the  
6 | Intron/Rebetol.

7 |                   We haven't recommended using that dose, and we  
8 | didn't bring the exact numbers with us.

9 |                   VOICE: We have it by drug.

10 |                   DR. ALBRECHT: We have it by drug? Okay. Can  
11 | you show that?

12 |                   No. That's not the one I want. That doesn't  
13 | help us, no. Thanks. You can take that off.

14 |                   DR. WOOD: The next question I have is for Dr.  
15 | Marzella of the FDA. During your presentation, you made  
16 | two comments. There was one slide that said that at 12  
17 | weeks it was predictive of whether or not individuals were  
18 | going to have a sustained virologic response, and then you  
19 | also alluded to 24 weeks. So, my next question is given  
20 | the data that we've heard, clearly the quality of life for  
21 | patients is compromised during therapy. Should there be a  
22 | recommendation that if patients have not responded by  
23 | either 12 or 24 weeks, that therapy should be discontinued  
24 | since they are unlikely to derive any further benefit from  
25 | it?

1 DR. MARZELLA: Yes, I think so. I would agree  
2 with that. I think that the label does make that  
3 recommendation. I think in actual practice there might be  
4 even more leeway and perhaps even shortening that. But I  
5 think in the label we have a cutoff of about 6 months.

6 DR. SCHWIETERMAN: It might be worth mentioning  
7 that with this particular product, the number of people who  
8 responded but had not reduced HCV viral load by 12 weeks  
9 was higher. In other words, if you were going to respond,  
10 you didn't always do it by 12 weeks with this product  
11 versus the other products, interferon, for example, with  
12 ribavirin or interferon monotherapy. You had close to 95  
13 percent of the patients by 12 weeks responding. Here it  
14 was closer. I think the number was 91 or something like  
15 that. So, 10 percent of the patients didn't do so until  
16 the latter half of the first 6 months.

17 DR. GULICK: Thank you.

18 DR. WEISS: Our label does indicate that  
19 patients be discontinued from therapy if the viral loads  
20 remain high. The label does indicate or suggest that if  
21 patients still have a high viral load after 24 weeks of  
22 therapy, that consideration should be given to  
23 discontinuation.

24 DR. GULICK: Thanks for that clarification.

25 Mr. Marco. I'm sorry. The sponsor.

1 DR. MCHUTCHINSON: It seems an appropriate time  
2 to show this data in relationship to this comment and which  
3 I mentioned also in terms of early stopping rules to  
4 discontinue therapy in those unlikely to respond.

5 This data shows the three treatment groups in  
6 this large 1,500 study in the ribavirin weight-based dosing  
7 group. It's a complex slide, but from the database,  
8 looking at week 12, or 3 months of treatment, HCV RNA, the  
9 prediction or the ability of week 12 HCV RNA to predict  
10 sustained response. You can see that patients who have not  
11 had a 2-log decrease, irrespective of the treatment arm,  
12 have very little chance of achieving a sustained response;  
13 whereas, patients who have alternative -- looking at it the  
14 flip side, the other way, patients who have a large more  
15 than 2-log reduction in therapy within the first 3 months,  
16 but they remain PCR positive because they've started off  
17 with very high viral load, have some chance of a sustained  
18 response, about 20 percent overall. And those who are PCR  
19 negative after 3 months of therapy have a much better  
20 chance of achieving a sustained response overall. So, I  
21 think this is important data in addition to the week 24  
22 data.

23 DR. GULICK: A follow-up question?

24 DR. KUMAR: Yes, a follow-up question. Do  
25 people with genotype 1 take longer than 12 weeks to

1 respond?

2 DR. McHUTCHINSON: Yes. There are a small  
3 group of individuals -- I don't recall the percentage off  
4 the top of my head -- in this trial who are what we call  
5 late responders to therapy. They lose HCV RNA between week  
6 12 or week 24, even some, a very few, after week 24 of  
7 therapy. They are usually the genotype 1 infected  
8 patients.

9 DR. GULICK: Mr. Marco and then Dr. Hoofnagle.

10 MR. MARCO: I guess my first questions are  
11 really for the agency, and everybody from Dr. Siegel, Dr.  
12 Schwieterman, or Dr. Weiss could answer this. But I sort  
13 of would like to almost know the ground rules and what  
14 questions are we allowed to ask.

15 For example, are we here just to truly discuss  
16 the weight-base dosing of ribavirin? Because as we see,  
17 the genie is out of the bottle and the combination has been  
18 approved. So, are we allowed to discuss questions about  
19 sort of the dose of the PEG either 1.0 or 1.5 and what  
20 really should be used?

21 DR. SIEGEL: Absolutely. Let me just make  
22 clear that we propose questions to an advisory committee.  
23 It is at the discretion of the chair who gets recognized  
24 and what can and should be discussed. We pose questions in  
25 those areas where we're seeking input, and the area you

1 mentioned is one of them. We've talked about postmarketing  
2 commitments both on interferon and on PEG-interferon dose.

3 We certainly appreciate input that you may feel  
4 is valuable to us in other areas that we might not have  
5 recognized the need for input or there are other areas  
6 outside the regulatory realm which can be discussed about  
7 these products that are less useful to us but many areas  
8 that you feel that we can contribute to, as far as we're  
9 concerned, we welcome.

10 MR. MARCO: No. I just asked that because  
11 we're even seeing here during this presentation, which was  
12 excellent, by Dr. Marzella, that there is some question  
13 about whether the PEG combo is actually more effective than  
14 standard interferon/ribavirin combination in certain  
15 patients.

16 But I guess my really only question is for Dr.  
17 Marzella. Even though you say in your conclusion number 5  
18 that there's not enough safety or efficacy data for  
19 PEG/ribavirin for weight-based dosing -- it just can't be  
20 drawn yet -- do you think that the postmarketing study that  
21 was designed with the agency, if it's done correctly,  
22 there's proper follow-up, could answer that question?

23 DR. MARZELLA: I think so. I think that the  
24 sponsor has really taken the commitment to heart to try to  
25 optimize dose. I think that while the study is run by an

1 | investigator, that the sponsor has committed enough  
2 | resources to ensure that not only the efficacy data, but  
3 | also the quality of the safety data will be such that we  
4 | will be able to make a risk/benefit assessment. So, there  
5 | is adequate power in the study and it's large enough to  
6 | also assess the safety concerns.

7 |           DR. GULICK: Let me just remind the committee  
8 | at this point this is a good opportunity to continual  
9 | informational questions, but let's try to avoid the  
10 | tendency to get into the discussion part, which we're going  
11 | to do after the open public hearing.

12 |           Dr. Hoofnagle and Dr. Wong.

13 |           DR. HOOFNAGLE: Well, I think you've nicely  
14 | documented the epidemic of obesity that's struck the United  
15 | States in the last 10 years.

16 |           (Laughter.)

17 |           DR. HOOFNAGLE: And yet, the very strange thing  
18 | about these data is how much improved therapy is. Even  
19 | standard interferon/ribavirin therapy has improved  
20 | considerably from your previous studies reported by  
21 | McHutchinson and Poynard. It is really quite striking, and  
22 | I wondered if you had an explanation. That was one  
23 | question.

24 |           But it goes to the central issue. The one  
25 | group that seems to have increased benefit from

1 PEG/ribavirin over standard ribavirin are patients with  
2 genotype 1 and low viral load, which is a very big  
3 surprise. But it's in that group where there is a very  
4 major increase in response rate. For instance, in the  
5 Poynard study, that group had a response rate of 36  
6 percent. In the current study, with standard interferon,  
7 that was 45 percent. I would say that that's significant  
8 improvement just with time. And with the PEG-interferon,  
9 that's 73 percent. Whereas, in all the other subgroups,  
10 and I know it's post hoc analyses, but these are analyses  
11 that have been somewhat routine since the original  
12 publications by Poynard and McHutchinson.

13 How do you explain that and how does this fit  
14 into your concept that the ribavirin dose was inadequate in  
15 this group? Does it seem to be adequate in the group of  
16 patients with low viral load? Is that the issue? Do you  
17 have an explanation for this major change?

18 DR. ALBRECHT: I agree with all of your  
19 observations, Dr. Hoofnagle. I had looked at the same  
20 thing and was very surprised. I have to tell you when we  
21 first analyzed the data and saw this 47 percent response  
22 rate in the Intron/Rebetol group, I was surprised because I  
23 was planning on about 42.

24 I think there's a factor that's occurring. We  
25 had a period of about -- what -- three years in between the

1 | Intron/Rebetol studies and this study, and I think what we  
2 | have is a greater comfort level with this particular drug.  
3 | As I mentioned to you, the dose discontinuation rates in  
4 | those first studies were 20 percent. If you look at this  
5 | study, we're looking at someplace between 13 and 14  
6 | percent. I think that in the very first study, we were  
7 | extremely worried about what we would see with the  
8 | combination of Intron/Rebetol and we were quick to  
9 | discontinue if we thought there was any problem.

10 |           So, I think what we have is a more experienced  
11 | set of investigators doing these trials. They were  
12 | routinely using Intron and Rebetol for the treatment of  
13 | their patients not in studies, and I think they were more  
14 | aggressive about dose reducing than stopping the drug. So,  
15 | I think that's why we're seeing these increased efficacy  
16 | rates in some of these populations.

17 |           I think the HCV-1/low viral load is very  
18 | interesting, and I agree with you. I cannot comment as to  
19 | why we see that. Although if you do look at the analysis  
20 | controlling for the weight, there doesn't seem to be a big  
21 | impact of the dose of ribavirin, and I can't explain that.  
22 | I think the best thing we're going to see is in a 4,000  
23 | patient study that we will see whether that indeed is  
24 | confirmed.

25 |           Dr. Koury, did you want to comment from a

1 | statistical point of view?

2 |           DR. KOURY: Yes. I don't have a backup slide  
3 | for this, but as you might have imagined, when we  
4 | investigated the attempt to control for ribavirin dose  
5 | using weight, we did lots of analyses to show that that  
6 | trend was similar across many different patient subgroups  
7 | and subtypes. One of the ways we helped to assess that is  
8 | in terms of calculating some odds ratios which estimate the  
9 | effect of a ribavirin dose when it's expressed this way.  
10 | The odds ratios are a little difficult to interpret, so I  
11 | have to give you a couple of them to try to put it in  
12 | perspective. But I think what was shown in the categorical  
13 | cuts was a little bit of an artifact of that particular cut  
14 | as opposed to using all the data and running the regression  
15 | analyses to estimate these effects.

16 |           For example, when we use all the patients, our  
17 | odds ratio for the ribavirin effect is 1.09, and now that  
18 | is expressed relative to a 1 unit increase on a milligram  
19 | per kilogram basis. But, for example, when we specifically  
20 | look at the genotype 1/low viral load, that odds ratio  
21 | actually increases to 1.2. So, we don't really have any  
22 | evidence that the effect of ribavirin is less in the  
23 | genotype 1/low viral loads. It may have been a bit of an  
24 | artifact of that particular cut of the data.

25 |           In fact, when we look beyond the 1.5 group but

1 | look in similar analyses which try to estimate the effect  
2 | of this ribavirin dose even in the other treatment groups,  
3 | which of course was partially controlled by weight, as Dr.  
4 | Marzella indicated, the odds ratio is exactly the same.  
5 | So, we have no evidence of really a different trend with  
6 | the ribavirin dose in the other interferon groups.

7 |           So, we think that there is still evidence of a  
8 | ribavirin effect no matter how we look at the data, and  
9 | that's one of our bottom line conclusions. There is a  
10 | tendency for association with ribavirin dose when expressed  
11 | as milligram per kilogram, but we have to be cautious about  
12 | looking at some of these subgroups, and we think that's  
13 | going to be the benefit of the postmarketing study which  
14 | will help us get enough patients in the various subgroups  
15 | to get better estimates of what the actual effect is when  
16 | you look at it by important prognostic factors.

17 |           DR. HOOFNAGLE: You know the dosing group of .5  
18 | microgram of PEG actually did weight-base both drugs, maybe  
19 | not as much as you wanted, but it did weight-base the  
20 | drugs. And was there not an effect of obesity or weight on  
21 | response rate in that group?

22 |           What I'm trying to say is that weight is an  
23 | independent predictor of a response to antiviral therapy in  
24 | this disease. It's true of many diseases, including  
25 | hepatitis B, and we don't know the reason for it. So, that

1 | would, it would seem to me, be the group that would best  
2 | show this effect.

3 |           DR. KOURY: Right. And in fact, this is  
4 | actually the figure that's shown in the Lancet paper  
5 | because it is the comparison of the regressions of the 1.5  
6 | to the .5 dose. So, the effect of the Intron weight  
7 | adjustment is accounted for. And you can see when the  
8 | ribavirin dose is expressed as milligrams per kilogram,  
9 | which is reciprocal of weight for the 1.5 dose but is a  
10 | little bit less clear for the other group, you can see the  
11 | same general trends. You see a clear dose response with  
12 | both components of the combination. The 1.5 is clearly  
13 | better because the line is above the .5. So, there's the  
14 | clear dose response for the PEG formulation, and we're also  
15 | seeing a ribavirin dose response that's suggested by this  
16 | analysis, again with the caveat that it's not based on a  
17 | randomized treatment assignment.

18 |           DR. HOOFNAGLE: And also with the caveat that  
19 | this Rebetol milligrams per kilogram is just a surrogate  
20 | for weight. That line can be drawn just with weight. You  
21 | don't need --

22 |           DR. KOURY: Well, it won't fit as well. It's  
23 | not quite a surrogate. Even the 1.5 group is reciprocal of  
24 | weight, and statistically it fits a little better than  
25 | simple weight.

1 DR. HOOFNAGLE: But the ribavirin dose was  
2 fixed, so it's not an independent variable.

3 DR. KOURY: Right. So, it's a reciprocal of  
4 weight. Reciprocal of weight and ribavirin dose expressed  
5 this way are statistically identical. But that's not true  
6 for the .5 group.

7 DR. SIEGEL: I'd like to address this concern  
8 because it's been one that we paid a lot of attention to,  
9 this concern raised by Dr. Hoofnagle.

10 It's true in the PEG/ribavirin arm that weight  
11 is essentially a perfect surrogate for ribavirin dose, and  
12 the 10.6 cut that you saw the data from is essentially a --  
13 75 kilograms divided by 800 is 10.6. And that's why we  
14 present the data 75 kilograms versus less.

15 There are major artifacts that occur when you  
16 compare, as you've seen in several of the Schering slides,  
17 the patients who are above or below 10.6 in different arms.  
18 Those arise from the fact that in the other two arms, there  
19 is both higher ribavirin, 1,000 or 1,200, and some level of  
20 weight adjustment. So, if I could call your attention to  
21 the top four slides on page 4 of the Schering handout, you  
22 can see in the first slide, which has a vertical line and  
23 it's at the 10.6 level. So, if you're looking at the  
24 heaviest patients, which are the ones to the left of that  
25 line, because again it's an inverse level -- they're

1 getting the lowest of Rebetol per body weight. You're  
2 talking about two-thirds of the patients on the  
3 PEG/ribavirin arm, or 320 out of the 500, and a very, very,  
4 very few percentage of patients from the other arm. You  
5 see just those few dots. It represents about 25 patients  
6 total. When you break them down by genotype, you get to  
7 their fourth slide, you see a 50 percent response rate in  
8 those patients less than 10.6. That represents 3 of 6  
9 patients.

10           The weight surrogacy is different, therefore,  
11 in each of these arms. What you're looking at in the  
12 Rebetol arm, when you look at less than 10.6, is people who  
13 weighed more than 75 kilograms, or 165 pounds about. In  
14 the other arm, you're looking at people who weighed more  
15 than 113 kilograms, or about 250 pounds. So, in the second  
16 and third graphs, if you look at the middle bar pairs, if  
17 you're comparing a 50 percent rate to a 27 percent rate,  
18 you're comparing people who weighed more than 75 kilograms  
19 on one arm to people who weighed more than 113 kilograms on  
20 another arm.

21           Aside from the artifacts that arise from  
22 confounding by weight, in this case you're also confounding  
23 by interferon dose because in that arm, interferon was not  
24 weight-adjusted either in the Intron arm. So, lower  
25 effects in patients who got less Rebetol could be because

1 they weigh more, as you pointed out. It could be because  
2 they got less interferon per body weight, or it could be  
3 because they got less ribavirin per body weight.

4 But also, aside from those multiple  
5 contributions, you're talking about nonrandomized  
6 comparisons. You're talking about one subset of the  
7 patients in one arm to the another subset of patients on  
8 the other arm. That does some oddly artifactual things,  
9 and the top right slide on page 4 can point out those  
10 artifacts. The net treatment effect between the two arms  
11 on this slide is 54 versus 47. It's a 7 percent effect.  
12 That's because of the modified response rate which includes  
13 people who are outside the predefined window. It would be  
14 6 percent, as you know, if you look at the defined.

15 In the overall population, though, you're  
16 looking at a 7 percent treatment effect. This is the next  
17 slide in your presentation, if you want to be able to  
18 project it.

19 But then when you subset that into these two  
20 groups, which are not comparable subsets, you have a 7  
21 percent effect here, and then you divide each of these  
22 groups into two groups, but you divide them differently  
23 because of the dosing regimen. You see in one group it's a  
24 23 percent difference, and in the other group it's a 14  
25 percent difference. Well, those 23 and 14 percent

1 differences are apples and oranges. They're comparing  
2 different groups of patients. You can't have any subset of  
3 a total of 7 percent that gives you two subsets, one at 23  
4 and the other at 14, and when you put them together, you  
5 get a 7 except when you're throwing in different cut  
6 points.

7           So, those are some of our concerns with this  
8 analysis, the potential for weight interaction, the  
9 potential for interferon interaction. I think our overall  
10 gestalt, as explained by Dr. Marzella, is that there is  
11 some significantly suggestive evidence that a dose  
12 adjustment of ribavirin may get better response rates, and  
13 there is some suggestive evidence that it may get toxicity.  
14 But there's neither conclusive evidence on either of those  
15 points nor is there evidence as to whether the extra  
16 response rates, if they do occur, outweigh the extra  
17 toxicity. And that's where we see it.

18           I want to just come back and underline the  
19 point you said. Among the potential explanations, in  
20 addition to interferon, weight, and artifactual problems,  
21 it's this issue just of weight. You didn't see the data on  
22 all arms done by weight, but in all arms, heavy people do  
23 not as well as light people on the approved Intron regimen,  
24 on all arms in this trial and other trials as well.

25           DR. GULICK: This is a follow-up comment, I

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23 not as well as light people on the approved Intron regimen,  
24 on all arms in this trial and other trials as well.

25           DR. GULICK: This is a follow-up comment, I

1 take it?

2 DR. KOURY: Yes, I think so.

3 (Laughter.)

4 DR. GULICK: Okay.

5 DR. KOURY: And I think it's fair to say that  
6 we agree that there has to be a lot of care in interpreting  
7 these kinds of analyses because of the potential for  
8 residual confounding variables to influence these results.

9 So, what we did, in an attempt to try to  
10 understand whether other variables could explain these  
11 apparent treatment effects, we did this in a series of  
12 analyses in which case we compared PEG 1.5 to Intron while  
13 controlling for the ribavirin dose on a milligram per  
14 kilogram and then examining, one at a time, the effects of  
15 additional covariates such as genotype, baseline viral  
16 load, gender, and age, and the residual effect of weight.

17 What we can see in these cases are that the  
18 important prognostic factors, genotype and baseline viral  
19 load, remain significant. However, the treatment effects  
20 remain significant once those variables are accounted for  
21 in these regressions. Similarly, things like gender is not  
22 significant anymore and age is, although if you control for  
23 it, you still get significant treatment effects.

24 And then we just systematically stepped through  
25 this one at a time and did it with the PEG 1.5 versus .5,

1 getting similar results, and stepping through now combining  
2 the two control groups saying there's a little more data if  
3 we combine the .5 and the Intron -- they are very similar  
4 in their responses. We get very similar results.

5 If we step through to the next slide, what we  
6 did was say if we now simultaneously control for the key  
7 prognostic factors such as genotype and baseline viral load  
8 -- in the first case, genotype is in the model, and we  
9 looked at the others one at a time. In the second case,  
10 genotype and viral load are in the base model, and we  
11 looked at the residual effects then of gender and weight  
12 and so forth. And we're getting consistent conclusions,  
13 that these other known variables don't really explain away  
14 the treatment differences, and yet they do seem to account  
15 for whatever the apparent gender and weight effects were in  
16 the univariate data.

17 So, again, you got to be careful, but we think  
18 we've looked at some of the usual suspects here and they  
19 don't really explain what we see in the data.

20 DR. GULICK: Let me stop for a second. Drs.  
21 Wong, DeGruttola, Seeff, and Mr. Marco have all raised  
22 their hands. Do any of you want to directly address this  
23 point before we move on to other points? Dr. DeGruttola  
24 first.

25 DR. DeGRUTTOLA: I just had a question here. I

1 think that Dr. Siegel did raise the important question of  
2 residual confounders. You basically have noncomparable  
3 subgroups, and you've shown that you've tried to look for  
4 some of these residual confounders. I'm wondering if you  
5 just did any subgroup analyses, similar to what the FDA  
6 did, just based on weight rather than the dose issue so  
7 that you do have comparable subgroups in those analyses and  
8 don't have to worry about all the residual confounders that  
9 you may or may not be able to identify.

10 DR. KOURY: Well, there would still be some  
11 potential confounding by weight because we didn't randomize  
12 that way either, and our impression of the data was that  
13 the ribavirin, when it's expressed as milligram per  
14 kilogram, explained the apparent effect of weight and  
15 gender. But we didn't actually do the same series of  
16 analyses using weight as the covariate.

17 DR. DeGRUTTOLA: I'd have to say that I think  
18 that if you just use weight as the covariate, then you have  
19 comparable subgroups. So, in the FDA's analyses, they're  
20 easier to interpret than when you have noncomparable  
21 subgroups and a lot of factors being entered in, the main  
22 one I think Dr. Siegel mentioning that you have very heavy  
23 people in one group compared to only moderately heavy  
24 people like me in another group, and they may not be  
25 comparable, and understanding how to do appropriate

1 adjustments for that situation I think can be complex. So,  
2 again, the question was just about if there are analyses  
3 just done by weight, which I think would be of interest to  
4 see.

5 DR. SIEGEL: Just as a quick comment, since we  
6 did a lot of those analyses. Certainly for the overall  
7 treatment effect and in many of the critical effects, when  
8 you subset by weight, the treatment differences between the  
9 interferon/ribavirin and between PEG-Intron/ribavirin tends  
10 to remain in the 5 to 7 percent rate in both heavy patients  
11 and light patients. You see both rates higher in the  
12 lighter patients and lower in the heavy patients, but the  
13 rates tend to run in that range.

14 DR. KOURY: But that doesn't totally control  
15 the ribavirin dose because in the Intron group, the heavier  
16 weight patients got an even higher dose of ribavirin.

17 DR. SIEGEL: You're absolutely right.

18 DR. KOURY: So, the trouble is you can't do it  
19 both, and that's the fundamental dilemma. So, we agree  
20 that things have to be looked at cautiously and we think  
21 this is pointing us into a direction. We agree that the  
22 postmarketing studies will provide substantial additional  
23 information to help further characterize what's going to  
24 happen in the important subgroups.

25 DR. GULICK: Mr. Marco, did you have a follow-

1 up?

2 MR. MARCO: No. It was basically I wanted a  
3 number because it looks like approximately 70 percent of  
4 the patients in the study had genotype 1 and approximately  
5 30 percent had less than 2 million copies of virus. So,  
6 how many are we talking about that were genotype 1/low  
7 viral load out of the approximately 1,500?

8 DR. ALBRECHT: I think I mentioned this when I  
9 talked about it. I said when you're talking about  
10 genotype/1 low viral load, you're talking about probably  
11 about 10 percent of the total population. It's about 18  
12 percent of the HCV-1 patients. I'm referring to the 1.5 in  
13 the Intron A groups. There's about 90 patients in each  
14 group.

15 DR. GULICK: I have Dr. Wong, Dr. Seeff. Then  
16 we're going to need to move on.

17 DR. WONG: I'm going to return to a request for  
18 information.

19 DR. GULICK: Thank you.

20 DR. WONG: I don't really have a good handle on  
21 the safety profile of ribavirin with respect to dose. The  
22 data you showed for a general summary of adverse events was  
23 just one table that summarized the events in which there  
24 was a greater than 10 percent difference between groups.  
25 Could you just give us a little more information about just

1 | what is the safety profile for ribavirin at various dose  
2 | levels, not just in this study but in the previous studies  
3 | you've done also, so we have a better idea, as we go up in  
4 | dose, what sorts of things would be expected to be seen?  
5 | And then where does the combined exposure to interferon  
6 | plus ribavirin fit into this?

7 | DR. ALBRECHT: Can we have master backup number  
8 | 18, which are the most frequent adverse events?

9 | I think there are a number of questions I think  
10 | here that I'll try to answer one at a time, and if I'm not  
11 | answering them, please help me with what you asked.

12 | I think one of the questions that we need to  
13 | answer is that the defining toxicity for ribavirin is  
14 | hemolysis. And there are really two components here. As  
15 | the dose of ribavirin increases, the amount of hemolysis  
16 | increases. We've seen that in our studies where we looked  
17 | at lower doses of ribavirin. So, you do see a proportional  
18 | increase in the hemolysis.

19 | The other part of the hemolysis question is  
20 | that it's very much a concept of baseline hemoglobin. If  
21 | you start with a low baseline hemoglobin, you're more  
22 | likely to go down below 10 grams per deciliter or to the  
23 | 8.5. What we see is there's a very high incidence for need  
24 | for dose reduction in those patients with low baseline.  
25 | Women at 12 grams are particularly susceptible. You get a

1 man in at 16 or 18 grams, they usually go through the study  
2 with no dose modification. So, hemolysis is the defining  
3 toxicity for ribavirin.

4 As I mentioned earlier, neutropenia from a  
5 laboratory side effect for the alpha interferons is  
6 certainly defining. Almost everybody has a drop in their  
7 white count. Almost everybody has neutropenia, and again  
8 it is baseline dependent. If you come in with a lower  
9 baseline, you are more likely to reach the levels I  
10 described for dose reduction.

11 Now, if you look at the slide that I showed  
12 you. I had showed you a slide on the dose reduction and  
13 the dose discontinuation. There does not seem to be an  
14 interaction between the dose of PEG and ribavirin for  
15 hemolysis. There doesn't seem to be any increase. There  
16 is a slight increase in the need for dose modification when  
17 you look at what we used as greater than 10.6 milligrams  
18 per kilogram of ribavirin with the PEG 1.5. There seems to  
19 be a small increase in the need for dose modification for  
20 neutropenia. So, we're going to find out in our 4,000  
21 patient study whether an interaction is really there, and  
22 we'll be looking at that very carefully.

23 There's an abstract been submitted to DDW that  
24 at the moment has got several thousand patients in it, and  
25 we don't seem to see an increase in neutropenia or

1 hemolysis with the high dose of PEG.

2 Now, subjective side effects. With alpha  
3 interferons, one of the things that we worry the most  
4 about, as I mentioned, are psychiatric side effects. In  
5 the group of psychiatric side effects, or the way they're  
6 classified, there are a number of things. Depression. It  
7 occurs in about 30 percent of patients. We did look at our  
8 database based on ribavirin dose, and we can't see that  
9 there's an exacerbation of depression with the addition of  
10 ribavirin.

11 We do see insomnia. Going back to the studies  
12 that we did in 1998 when we received the license for Intron  
13 A/ribavirin, I think Dr. Schwieterman will remember better  
14 than anyone else, we see an increase in insomnia when we  
15 add ribavirin. This is consistent with it being a  
16 nucleoside analogue. So, in that psychiatric category, we  
17 see an increase in insomnia when we add ribavirin. It's no  
18 different when we use it with PEG. We see the same thing.

19 I think this doesn't exactly address your  
20 question, but it does help you see again where the  
21 differences between the drugs are. What we did here is we  
22 looked at most frequent adverse events. That's any adverse  
23 event that occurred in more than 10 percent of patients.

24 In these large trials, the way you collect  
25 adverse events is the following. You ask the patient at

1 every visit, have they had any problems since the last  
2 visit and try to get them to tell you how they feel and  
3 what they've experienced. That is then assessed by the  
4 physician and graded as to severity. The other thing that  
5 we do at each visit, which probably prompts side effects,  
6 is we say to them, well, last time you had X. How are you  
7 doing? Is it any worse? Is it gone? Whatever, and we  
8 actually record this data. So, what we see are treatment  
9 emergent side effects that we report. If you had an  
10 appendectomy while you're in the study, that's a treatment  
11 emergent side effect. So, we have lots of side effects  
12 reported.

13 What this shows are side effects that occurred  
14 in more than 10 percent of patients and for which we could  
15 see a difference based on the ribavirin dose, when we  
16 adjusted for dose over here, and between the two major  
17 treatment groups, as studied. As I indicated before, flu-  
18 like symptoms or body as a whole, as we call them,  
19 asthenia, fever, rigors, arthralgia, myalgia. I will  
20 mention that asthenia is a uniquely European term basically  
21 for the flu-like symptoms and those kinds of things. You  
22 can see the increase in the PEG doses.

23 I would mention to you here there seems to be a  
24 higher incidence of asthenia with the increased ribavirin  
25 dose. We'll have to find out if that's true in the new

1 study.

2 GI side effects are clearly related to the PEG  
3 dose. We don't seem to see any effect really when we use a  
4 higher ribavirin dose.

5 DR. WONG: Could I just interrupt for a second?  
6 I guess what you're showing us again is the subgroups based  
7 on dosage versus body weight in this study, but you must  
8 have done some preliminary dose-finding studies just with  
9 ribavirin before you ever got to this study. I guess  
10 that's really what I was hoping to see. What's the safety  
11 profile? Can you just give a brief summary of the safety  
12 profile of ribavirin as a drug per se without interferon to  
13 begin with? Then put that into the context of the studies  
14 with interferon.

15 DR. ALBRECHT: I guess I could ask maybe Dr.  
16 Hoofnagle to give you a profile of ribavirin as  
17 monotherapy. As you probably know, ribavirin as  
18 monotherapy does not have activity in the treatment of  
19 chronic hepatitis C.

20 DR. WONG: No, I understand, but it has a  
21 safety profile.

22 DR. ALBRECHT: Right. But there were some  
23 studies done early, one of them that Dr. Hoofnagle did,  
24 where they looked at ribavirin monotherapy. So, Jay, would  
25 you mind kind of summarizing that?

1 (Laughter.)

2 DR. HOOFNAGLE: The studies that we did were  
3 quite small really. You do see hemolysis even at 600  
4 milligrams. It's usually quite mild. We were never brave  
5 enough to go above 1,200 milligrams because the hemolysis  
6 becomes considerable.

7 But in the early studies, everybody received  
8 1,200 milligrams of ribavirin with interferon, and it was  
9 Schering that introduced this idea of the two levels of  
10 1,000 versus 1,200, which is reasonable because if you use  
11 the higher dose, you'll have to start reducing the dose in  
12 these small weight patients.

13 But I wondered whether Schering had data on  
14 just pharmacokinetics. Instead of doing a big study, 4,000  
15 patients with all these dosings, can't you do a small study  
16 with pharmacokinetics showing what would be the appropriate  
17 dose in different sized people? Wouldn't that be so much  
18 easier?

19 DR. LAUGHLIN: We actually can address that two  
20 different ways. If I could have slide number 20 first.  
21 Perhaps to get directly to your question, this may be the  
22 best way to get to it.

23 DR. WONG: I like that question. I've been on  
24 this committee for quite a few years now and I can say that  
25 this is the first time I've ever received a briefing book

1 that didn't give a general introduction on the drug, its  
2 pharmacology, its experience in preclinical and early  
3 clinical trials, et cetera before getting into a big 1,000  
4 subject comparative treatment trial in which my ability to  
5 try to dissect out what's the safety and efficacy of the  
6 individual components of a combination therapy -- I  
7 couldn't do it.

8 DR. LAUGHLIN: Let me try and address it at  
9 least with the specific toxicity of anemia. As we said,  
10 because there's not an indication, at least in hepatitis or  
11 in this population, to look at ribavirin monotherapy, it  
12 has to be in the context of co-administered interferon.

13 If you look in this study, this is a dose-  
14 finding study which was conducted with about 40 subjects  
15 per group either with placebo, 400, 600, 800, or 1,000 to  
16 1,200 milligrams of ribavirin. Again, if you just focus on  
17 antiviral effect, the antiviral effect measured at 12  
18 weeks, in terms of what was the magnitude of viral  
19 reduction, there's an increase in that efficacy. Not  
20 surprisingly, there's also a price to pay in terms of  
21 reduction in hemoglobin. This is probably the best data  
22 that will tell you what is the isolated ribavirin toxicity,  
23 and here it's measured primarily --

24 DR. WONG: And this is really the parameter  
25 that we should focus on. Anemia is the dose-limiting