UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTIVIRAL DRUGS ADVISORY COMMITTEE

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THURSDAY

NOVEMBER 14, 2002

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The Advisory Committee met in the Versailles Room in the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, 15 8:30 a.m., Roy Gulick, M.D., M.P.H., Chair, presiding

PRESENT:

ROY M. GULICK, M.D., M.P.H., Chair

TARA P. TURNER, Pharm. D., Executive Secretary

JANET A. ENGLUND, M.D., Committee Member

COURTNEY V. FLETCHER, Pharm. D., Committee Member

PRINCY N. KUMAR, M.D., Committee Member

SHARILYN K. STANLEY, M.D. (by phone), Committee Member

LAUREN V. WOOD, M.D., Committee Member

EUGENE SUN, M.D., Acting Industry Representative (non-voting)

MIRIAM J. ALTER, Ph.D., Consultant

THOMAS R. FLEMING, Ph.D., Consultant

VICTORIA A. JOHNSON, M.D., Consultant

MARIA H. JOGREN, M.D., Consultant

SAMUEL SO, M.D., Consultant

BRIAN WONG, M.D., Consultant

LILLIAN THIEMANN, Patient Representative (non-voting)

JAY H. HOOFNAGLE, M.D., HHS Federal Employee (non-voting)

I N D E X

P R O C E E D I N G S

8:35 A.M.

DR. GULICK: Good morning, everybody. I'm Trip Gulick from Cornell University in New York and I'm pleased to call to order this meeting of the Antiviral Drugs Advisory Committee.

I'd like the members of the Committee to introduce themselves. Please state your name and your affiliation for the record. And we'll start with Dr. Sun.

DR. SUN: Eugene Sun, Abbott Laboratories.

MS. THIEMANN: Lillian Thiemann, Visionary Health Concepts and the Women's HIV Collaborative of New York.

DR. HOOFNAGLE: Jay Hoofnagle with the Division of Digestive Diseases and Nutrition, NIDDK, NIH.

DR. SO: Sam So from Stanford University.

DR. ALTER: Miriam Alter from the Division of Viral Hepatitis, Centers for Disease Control and Prevention.

DR. JOHNSON: Victoria Johnson, Infectious

Diseases, UAB.

DR. ENGLUND: Janet Englund, Department of Pediatrics, University of Washington.

DR. GULICK: On the telephone we have Dr. Stanley. Can you hear us Sharilyn?

DR. STANLEY: Yes, good morning, Trip, here I am.

DR. GULICK: Okay, and just state where you're from.

DR. STANLEY: Texas Department of Health.

DR. GULICK: Thanks. Thanks for joining us.

DR. FLETCHER: Courtney Fletcher, Department of Clinical Pharmacy, University of Colorado Health Sciences Center.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. WOOD: Lauren Wood, HIV and AIDS Malignancy Branch, NCI, NIH.

DR. WONG: Brian Wong, VA Connecticut Health Care System and Yale University.

DR. KUMAR: Princy Kumar, Georgetown

University, Washington, D.C.

DR. FLEMING: Thomas Fleming, University of Washington.

DR. PETRICOIN: Emanuel Petricoin, CBER, FDA.

DR. TAUBER: Bill Tauber, FDA, CBER.

DR. MARZELLA: Lou Marzella, Division of Clinical Trials, CBER.

DR. SIEGEL: Jay Siegel, Office of Therapeutics at CBER.

DR. GULICK: Thanks, everyone. To start off, I'd like to call on Dr. Deborah Burncraft of the Agency who would like to say a few words.

DR. BURNCRAFT: Good morning. I'd like to acknowledge Dr. Brian Wong's service on the Antiviral Drugs Advisory Committee. Dr. Wong is Associate Professor of Medicine at Yale University School of Medicine and Chief of Infectious Diseases at the VA Connecticut Health Care System.

Dr. Wong has served on this Committee in an exemplary fashion since 1998, providing input and insight on some very difficult and interesting

deliberations that we've had. So today, we'd like to recognize your service with a letter of recognition and a certificate of appreciation and a placque will be coming to you and we look forward to working with you as a consultant.

Thank you very much for all of your help.

DR. WONG: Thank you.

(Applause.)

DR. GULICK: Brian, I can add that we will miss your uncanny ability to cut through things and straight takes on the questions and issues.

Okay, Tara Turner will read the Conflict of Interest Statement.

DR. TURNER: Thank you. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

All Committee Members and consultants have been screened for conflicts of interest with respect to the products at issue, competing products and their sponsors. The reported financial interests have been

evaluated and it has been determined that the interests reported by the participants present no potential for a conflict or the appearance of such at this meeting with the following exceptions.

Dr. Thomas Fleming has been granted a waiver under 18 USC 208(b)(3) for his participation on a data safety monitoring board for a competitor to Pegasys, peginterferon alfa-2a and Copegus ribavirin on an unrelated matter. He receives less than $10,001 a year.

Dr. Princy Kumar has been granted a waiver under 18 USC 208(b)(3) for her participation on a scientific advisory committee for a competitor to Pegasys and Copegus. She receives less than $10,001 per year. Dr. Kumar has also been granted a waiver under 21 USC 355(n)(4), amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in a competitor to Pegasys and Copegus. The stock value is less than $5,001.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of

the Parklawn building. We would also like to note that Dr. Eugene Sun is participation in today's meeting as the Acting Non-voting Industry Representative.

With respect to FDA's invited non-voting patient representative, Ms. Lillian Thiemann, has reported interests that we believe should be made public to allow the participants to objectively evaluate her comments. In the past, Ms. Thiemann has received grants from Amgen, Roche and Schering for hepatitis C virus educational programs. In the event the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

Thank you.

DR. GULICK: Thanks very much. Dr. Karen

Weiss from the Agency will make a few introductory remarks for this morning's meeting.

DR. WEISS: Good morning. I just also want to extend my welcome to the Committee and to the public and to thank you all in advance for what I know will be a very interesting discussion later this afternoon.

One of the reasons we're here, there are a number of reasons why, but almost a year ago in December of '01 we updated this Committee on another interferon based therapy for the treatment of chronic hepatitis C infection and we had a very, I think, vigorous and useful discussion and at that time the Committee and members of the public all asked that next time applications come before this Committee that we bring them to the Committee a little bit earlier in the process so that there will be a time for additional input as the FDA goes through its processes. And so we heard that message. We appreciate that there is a large amount of interest in the community for products intended for the treatment of hepatitis C infection. There are a lot of

interesting questions and we look very forward to your input and to the discussions.

I think that Hoffman-LaRoche is to be commended for coming to the Committee and bringing to the Agency such a thorough and extensive application and evaluation of their combination of Pegasys, Copegus for the treatment of patients with hepatitis C infection and then lastly, this review was a joint effort between numerous individuals from the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research, brought together experts from a number of different disciplines who came together in this collaborative effort to review this application and those people are all too numerous to tell you all their names, but I want to thank everybody for all their hard work and with that I would like to then just introduce Emanuel Petricoin who will bring to you some introductory comments about this application.

DR. PETRICOIN: Good morning. I'll be talking over the next 5 to 10 minutes or so about the biologic component of this submission, the Pegasys

component which is comprised of a pegylated interferon. The interferon alpha-2a biologic is recombinant, human leukacyte interferon produced in E.coli. Molecular weight approximately 19,000 Daltons. The pegylated moiety is approximately 63,000 Daltons. This is a lysine based pegylation, that is the pegylations occur on the lysines of the interferon molecule and therefore the molecule itself is comprised of multiple isoforms.

All of the critical components that produce this compound have been inspected by the FDA within the last several months and all outstanding inspection and CMC issues have been resolved and they were minor to begin with. Inspection of Roche Penzburg facility occurred in July. This is for the Pegasys molecule that's been approved recently. The critical component, the pegylation entity itself manufactured by Shearwater has been extensively reviewed and the compounding that takes place at Nutley in the formulation of the product itself was recently inspected in August on all outstanding and minor issues that were noted at the time have been

resolved prior to the approval of the Pegasys molecule itself.

Now there were changes in manufacturing that took place after the critical Phase III trial. These changes were made to the product and manufacturing to address the market supply and the critical market supply issues that would have to then be addressed going forward. These changes require evaluation of analytical comparability in pharmacokinetic profiles. Now at that time, PK comparability was not demonstrated. However, through thorough and rigorous evaluation by Roche who is to be commended for their rigorous evaluation of the molecule and a lot of hard work by the Agency working with Roche, it was determined that product specifications could be tightened and a new PK trial was performed that then compared the Phase III material to the commercial product that was made under tightened specifications.

The result of this trial demonstrated comparability at the PK level for the Phase III material compared to the commercial product.

We reviewed the time line for the BLA/NDA for the Pegasys component. We received this application May 22, 2000. A complete response letter was issued April 10, 2001. The PDUFA goal date for this was April 12, 2001.

For the PK trial, meeting and consultations between CBER and the sponsor for the clinical trial to evaluate PK comparability was initiated and completed between April 2001 and April 2002. So this is when Roche went back, worked with the Agency, redid a PK trial to demonstrate comparability under tightened specifications that was then demonstrated. A complete response to the complete response letter was received April 16, 2002. The PDUFA action goal date was October 16, 2002 and the application was approved on that date.

The peginterferon alpha-2a, the Pegasys component and the co-Pegasys was received June 3, 2002 with the PADUFA action goal date December 3, 2002.

Conclusions are this time for the molecule, the CMC part of this presentation for Pegasys, changes in manufacturing were made after

Phase III trials to address market supply, required further demonstration of PK comparability to the commercial product.

The Agency worked with Hoffman-LaRoche as they thoroughly evaluated the PK and analytical data. Based on this, product specifications were tightened to ensure product consistency, robustness of the process and PK equivalency. That was demonstrated. And all CMC issues and pre-approval for Pegasys inspection items were resolved.

For the ribavirin component, there's still some small outstanding issues, a small amount of data for the NDA still needs to be submitted and reviewed and that's on-going and shouldn't cause any problems for the final product.

I'll take any questions at this time.

DR. GULICK: Can you just help the Committee with the abbreviation PDUFA?

DR. PETRICOIN: Certainly. That's the Prescription Drug User Fee Act. These are milestones that are Congressionally set so that we meet some type of deadline that is a reasonable amount of time to

review all the data, the product data, the pharmacokinetic data, the clinical data for any product that's submitted to the FDA.

DR. GULICK: Thanks. Are there other questions for Dr. Petricoin?

Dr. Sjogren?

DR. SJOGREN: I have a question. I saw in one of your slides that the pegylated product is 63 kiloDalton. We've grown accustomed to seeing 40 kiloDalton in presentations at major meetings. Is that a significant difference? Why 63 kiloDalton in your slide and why 40 kiloDalton in other presentations?

DR. PETRICOIN: The peg moiety itself is 40 kiloDalton, the final product, the interferon which is about 20 kiloDalton and then the peg component comprise about a 60 kiloDalton final molecule.

DR. SJOGREN: So it's the sum of both. Thank you.

DR. GULICK: We are going to have plenty of time for questions after the morning presentations. Are there any other burning ones for Dr. Petricoin at

this time?

Okay. Thank you.

Great, we'll move to the sponsor presentation from Hoffman-LaRoche.

(Pause.)

DR. TEUBER: Hi, good morning. Thank you very much, Dr. Gulick and good morning to FDA, Members of the Committee. My name is Dr. Candace Teuber and I'm the regulatory leader for Pegasys. On behalf of Roche, we're pleased to present to you today our Pegasys, peginterferon alpha-2a and Copegus, Roche's ribavirin in combination therapy development program.

The combination therapy development program was submitted to FDA as a BLA for Pegasys and an NDA for ribavirin in June of this year as mentioned by Dr. Petricoin.

We'd also like to mention that we'd like to thank FDA for acknowledging the collaborative efforts and hard work that went into working together for the monotherapy application and also in working together for the combination application in making it today to the Advisory Committee.

The approved indication for Pegasys monotherapy is as follows on the slide. Pegasys peginterferon alfa-2a is indicated for the treatment of adults with chronic hepatitis C who have compensated liver disease and who have not been previously treated with interferon alpha.

Patients for whom efficacy was demonstrated included patients with compensated cirrhosis. Also, the approved dosage and administration for Pegasys and monotherapy is 180 micrograms administered subcutaneously once weekly for 48 weeks.

And we're before the Committee today to seek approval for Pegasys and Copegus in combination to expand this indication as follows:

For Pegasys peginterferon alpha-2a in combination with Copegus ribavirin for the existing monotherapy indication.

In addition, the data we'll be presenting to the Committee also supports an expansion of the dosage and administration section for a modification of the treatment duration of ribavirin dose according

to the important prognostic factor of genotype.

In looking at the regulatory history of the application, the USIND was submitted in July of 1998 and subsequent to the IND filing, we had several key interactions with the Agency including an end of Phase II meeting, the granting of fast track designation, a pre-BLA/NDA meeting with both -- jointly with CBER and CDER which resulted in the filing of the NDA and BLA applications in June.

As mentioned previously in the presentation and also by Dr. Petricoin, monotherapy for Pegasys was approved on October 16th this year and we're before the Committee today to seek approval for Pegasys and Copegus in combination for hepatitis C.

Our presentation will begin with an overview of the Pegasys and Copegus development program by Dr. Joe Hoffman. Dr. Hoffman is the Vice President and Group Leader for Virology and Transplantation Clinical Development at Roche.

Our Phase III findings from our two pivotal trials will be presented by Dr. Frank Duff and Dr. Duff is the Clinical Leader for the Pegasys

Development Program.

Dr. Jonathan Solsky, our Director of Drug Safety and Risk Management, will be presenting the safety findings in the trials and Dr. Hoffman will conclude with a risk benefit assessment.

We also have two hepatology experts who are available for your questions today, Dr. Don Jensen, Director, Section of Hepatology, Rush Presbyterian St. Luke's Medical Center from Chicago, Illinois; and Dr. Mitch Schiffman, Chief Hepatology Section, Virginia Commonwealth University Health System, Medical College of Virginia in Richmond.

We also have several Roche experts who are available for questions, Dr. Mike Brunda from Clinical Science and Dr. Brunda was responsible for the design and analysis of our Phase III trials; Ms. Celine Eliahou, our toxicologist; Ms. Amy Lin, our statistician; and Drs. Matthew Lamb and Karin Jorga from Clinical Pharmacology. And with this, I'd like to turn the presentation over to my colleague, Dr. Hoffman.

DR. HOFFMAN: Thank you, Candace. Over

the next few minutes, I'd like to give you a rationale for the development of Pegasys, briefly review the clinical program and then discuss dose selection in the combination therapy program.

We first began developing Pegasys back in 1997, the only approved therapy for chronic hepatitis C was standard interferon three times per week. What I've shown here are some of the results that could be expected with that therapy. These actually come from our monotherapy program from the control arms. And what you can see here with sustained virological response on the Y axis, overall responses of less than 20 percent; responses in genotype 1 are only about 7 percent; responses in cirrhotics about 5 percent; and in those patients with genotype 1 with either high viral load or cirrhosis, only about 1 to 2 percent.

A probable explanation for this is given on this slide which shows the activity time profile of interferon given three times per week and what you can see is following an initial dose, there's a rapid upstroke in activity, followed by a rapid downstroke such that between doses, there is no detectable drug

and it's during these times that the virus can rebound.

Pegasys was developed to overcome this limitation. What you see here is the interferon which is about 20 kiloDaltons, interferon alpha-2a, covalently bound to a branched 40 kiloDalton polyethylene glycol moiety.

This results in the maintenance of a soluble formulation that retains it's intermodulatory and antiproliferative properties and because of improved pharmacokinetics, has a sustained action provided both by a decreased clearance and an extended absorptive phase.

It has a relatively limited volume of distribution that allows for fixed dosing.

This is a concentration time profile for Pegasys and what you can see here is following a weekly dose that there's maintenance of concentration through the end of the dosing period, thereby maintaining antiviral pressure through that time.

Now I previously mentioned that the volume of distribution for Pegasys is relatively small, it's

smaller than that of other available interferons and what that results in is a relatively consistent clearance shown here for a broad range of weights, from 45 kiloDaltons up through 95 or 100 kiloDaltons. This consistent clearance results in relatively consistent concentration in the blood across weights and therefore allows for fixed dosing.

As has been mentioned, Pegasys as monotherapy was approved last month and I'm only going to go over results as they pertain to the combination program. Within that program of monotherapy, we did four studies, a dose finding study in Phase II, non-cirrhotic patients, a powered study in patients with cirrhosis and then two, pivotal Phase III trials, one versus standard interferon and one versus an induction regimen of interferon.

In that program, there were 1600 patients, approximately 1,000 received Pegasys and about 600 received the control.

So what's the appropriate dose of Pegasys? Our first trial was a Phase II study, proof of concept, dose finding trial in patients without

cirrhosis. And what we did was to compare interferon alpha-2a, three million units three times per week to four weekly doses of Pegasys; 45, 90, 180 and 270 micrograms. And what you can see here is that all of the doses, all of the dose groups of Pegasys had a higher sustained virological response than the interferon which was only 3 percent and that there was a dose response from 45 up to 180 micrograms. Importantly, at a higher dose of 270 micrograms, there was a plateauing of the effect and there was an increase in the need for dose modification.

So the two highest responses were seen at 90 and 180, 30 and 36 percent. But when you looked closely at this, more closely and look at it by response to genotype 1, what you see is that in 180 microgram group, the response was 31 percent versus only 14 percent in the 90 microgram group. So these results were very encouraging, but also indicated that 180 micrograms was the appropriate dose.

The second trial that we conducted was a power trial in patients with cirrhosis. Again, we used interferon alfa-2a, three million units, three

times per week as the control. And this time we looked at two weekly doses of Pegasys, 90 and 180 micrograms. We used the 90 microgram dose group in this trial as well because as everyone here knows, patients with cirrhosis tend to be older, tend to be sicker, can be more medications, so we wanted to have a back up dose in this population.

Once again, in both of the Pegasys dose groups, the responses were higher than in the control. Eight percent in the control; 15 percent in the 90 microgram and 30 percent in the 180 microgram group. Importantly, only the 180 microgram group achieved statistical significance in terms of superiority to the control.

Once again, very encouraging results in a difficult to treat population and again indicating 180 micrograms to be the appropriate dose. Now in one of two phase 3 trials we inserted a 135 microgram arm, the purpose of which was to investigate a step down dose between 90 and 180. Once again the control arm, interferon alpha-2a, three million units, three times per week and what you can see here are the results,

both the 135 and the 180 microgram dose groups achieved statistical superiority over the control group. The sustained virologic responses at week 72 were not different. However, if one looked at interim virological points here the week 24 is shown, there was a consistency in higher responses in the 180 microgram group.

In addition, we looked at histology. It was only the 180 microgram group that showed statistically significant improvement over the interferon control.

From a safety standpoint, what you see here for 135 and 180 are major safety findings, severe AEs, serious AEs including treatment related, AEs in laboratory abnormalities resulting in withdrawal and AEs in laboratory abnormalities resulting in dose modification. The numbers are very similar, a slight increase here in the 180 microgram group in terms of dose modifications. However, it's important to point out that these patients were generally dose reduced to 135 micrograms while these patients were generally reduced to 90 micrograms which is clearly a

suboptimal dose.

Based on these and other data, the 180 microgram dose was approved in Pegasys monotherapy in the United States and elsewhere.

And just to summarize the results of the monotherapy program, I've already shown you this slide of results with standard interferon and these are the result from our pivotal trials program. Once again, overall with Pegasys, 180 micrograms; 28 to 39 percent versus less than 20 percent; 22 to 28 percent versus about 7 percent in genotype 1; 30 percent versus approximate 5 percent in cirrhotics and in the difficult to treat, geno-1 high viral load and geno-1 patients with cirrhosis, 13 to 14 percent versus about 1 to 2 percent.

So very encouraging results including difficult to treat patients, but clearly a lot of room for improvement, especially down this end.

That's why we proceeded into a combination therapy program which is summarized here. The program consisted of three trials, a pilot safety study and then two registration trials that you'll hear about in

more detail today.

Before moving forward, just a few words about ribavirin. When combined with interferon, there is improved efficacy over interferon alone. It is teratogenic in animals and mutagenic and induces hemolysis.

The dose of 1000 or 1200 milligrams per day is safe and efficacious with standard interferon and is an approved regimen, Rebetron.

And the 1000 or 1200 milligram ribavirin dose was combined with Pegasys in the pilot safety study.

Now whereas the pharmacokinetic data did not support weight base dosing for Pegasys, it is reasonable to take weight into consideration in dosing ribavirin.

What you see here is a simulated exposure by body weight. Here you have the AUC according to body weight for a dose of a 1000 micrograms and what you can see is that as weight increases there is a drop with 1000 micrograms which would continue in that fashion at the higher weights. So what's done is that

the patients who weigh 75 kilograms or more, the dose is increased to 1200 milligrams which gives this step up and then a continued decline, but when one looks across a broad range of weights, there's a relatively narrow band of concentrations that are seen.

As I mentioned, we did a pilot safety study, represented here as the NV15800 trial in which we combined Pegasys 180 micrograms with 1000 or 1200 milligrams of ribavirin, Copegus. And based on the result, the safety results from that study, we moved into a comparative trial. In that trial, we went with the 180 microgram dose which for the reasons that I've explained in the monotherapy program combined with Copegus 1000 or 1200 milligrams. We chose that dose for three reasons. One, it was the approved dose of ribavirin with standard interferon. Secondly, it was the dose we had already investigated in the pilot study. And thirdly, we wanted to be able to compare the ribavirins across the two arms.

We also included Pegasys monotherapy dose so that we could investigate the effects of ribavirin on both the safety and the efficacy.

And you'll hear the results of that trial shortly, but what I wanted to mention though is that we felt it was important to do a companion study and that is because of these data which are a summary of the Rebetron registration data and what was established with Rebetron was that certain subgroups of patients, genotype 2,3 low viral load might be treated adequately with only 24 weeks of therapy rather than a full 48 weeks.

We wanted to a companion trial along with the comparative study to investigate whether we could reduce exposure without loss of efficacy in patient subgroups.

And these studies are tied together by a common arm which is the Pegasys 180 microgram group with full dose; Copegus, 1000 to 1200 milligrams.

Now designing this study there were three things we could change in looking at decreasing exposure. One was the duration of combination therapy which we thought was a primary way to go based on the Rebetron data, but also because in this way you decrease exposure to both of the components of the

regimen.

We also considered looking at a lower Pegasys dose or a lower Copegus dose. Because of the reasons I mentioned, we felt that 180 micrograms was the dose to move forward with, but with Copegus there certainly were data available suggesting that a lower dose might be adequate and safer.

So as I mentioned in the common arm for bridge, we selected the 1200 milligram dose per day and although there were no power dose finding studies of ribavirin, what was available in the literature and anectdotally suggested that 800 milligrams would be safer and might be adequate. However, 600 milligrams and lower might not be as efficacious and would provide relatively little safety advantage over the 800.

So in this second trial what we did was investigated the duration of combination therapy, 24 versus 48 weeks. We kept the Pegasys dose constant at 180, but varied the Copegus dose down to 800 versus the full dose.

So just to summarize what you're going to

hear now in terms of our program, the program was designed to evaluate the efficacy and safety of Pegasys and Copegus across genotypes versus Rebetron and versus Pegasys monotherapy. But importantly, it was also designed to evaluate the impact of shorter treatment duration on response in genotype non-1 and genotype 1 and also the impact of a lower Copegus dose on responses according to genotype.

And with that I will turn over the microphone to Dr. Frank Duff who will talk about the efficacy results from the combination trial.

DR. DUFF: Good morning, ladies and gentlemen of the Committee and the audience, the FDA. I'm pleased to have the opportunity to present the efficacy results from our two pivotal Phase III studies which Dr. Hoffman has introduced.

Beginning with study NV15801, our comparative trial versus Rebetron. The efficacy objectives are outlined on this slide. The primary objective was to compare the efficacy of Pegasys plus Copegus versus Rebetron; secondarily, to compare the efficacy of Pegasys plus Copegus versus monotherapy.

And finally, to compare the efficacy across treatment arms by HCV genotype.

This was a randomized study. It was open label for Pegasys and for ribavirin and it was blinded for Copegus versus placebo in the two Pegasys arms. It was stratified by country as well as by HCV genotype.

Patients were randomized to one of three treatment arms. The first, Pegasys 180 microgram given once weekly, plus Copegus in a standard dose of 1000 or 1200 milligrams a day using the 75 kilo weight split that Dr. Hoffman mentioned.

Patients were also randomized to receive Rebetron which is a combination of Intron A, 3 million international units given subcutaneously three times a week with Rebetol, again doses of 1000 or 1200 milligrams with the weight consideration at 75 kilos.

Finally, to Pegasys 180 micrograms, given subcutaneously, once weekly versus placebo. I should mention that this was a 2 to 2 to 1 randomization scheme and I should also mention that patients were treated for 48 weeks with 24 weeks of follow up and

our end points were determined at 72 weeks.

This study and the study that I will refer to next were conducted in North and South America, as well as in Europe, Australia and Asia.

The primary endpoint for this study was combined sustained virological response and sustained biochemical response at the end of follow up. Sustained virological response was defined as 2 negative PCR determinations and sustained biochemical response was defined as two normal ALT at end of follow up.

Our secondary endpoints included sustained virological response, sustained biochemical response and end of follow up histological response on a subset of 20 patients randomized to the study. The analysis population was all patients randomized.

Inclusion criteria included serological evidence of HCV infection, detectable HCV RNA with a lower limit threshold of 2000 copies per mil; evidence of elevated serum ALT; a liver biopsy consistent with chronic hepatitis C; evidence compensated liver disease defined as Child-Pugh grade A; having an age

greater than or equal to 18 years; and finally, being naive to interferon and to ribavirin.

Patients were excluded if they had evidence of decompensated liver disease defined as Child-Pugh grades B and C. They were also excluded from our pivotal studies if they had evidence of coinfection with HIV or HBV. They were excluded if they had evidence of anemia or an ability to tolerate anemia and finally, if they had any of several significant comorbid medical conditions that were outlined in the protocol.

Patient characteristics were well balanced across the three treatment arms and I've outlined major ones which have been identified with outcome in terms of sustained virological response. Two thirds of patients were genotype 1. HCV RNA titer was approximately 6 times 10^6. Twelve to 15 percent of patients had evidence of bridging fibrosis of cirrhosis at baseline liver biopsy. The mean age was approximately 42 years.

Patient mean weight evenly distributed approximately 79 kilos and finally, approximately 70

percent of the patients were male. I should also note that 85 percent of the patients randomized to the three treatment arms were Caucasian. Approximately 5 percent of patients were categorized in our trial as black and 5 percent as Oriental, the remaining 5 as other.

This slide reviews our premature withdrawals. Jonathan Solsky will spend considerable detail reviewing our safety. I wanted to just highlight some of our nonsafety reasons for withdrawal. I will point out that there were somewhat higher premature withdrawals on our Pegasys arm at 32 percent, that is Pegasys monotherapy, as well as our Rebetron arm at 32 percent. The premature withdrawal rate in our Pegasys plus Copegus arm was 22 percent and the primary driver for this difference is the category insufficient therapeutic response and I wanted to point this out because in this study patients who had not achieved evidence of a sustained virological response, I should say of a virological response by week 24 were given the opportunity to leave the study, if they wished and were categorized

as nonresponders. And this occurred somewhat more frequently in the Pegasys monotherapy arm and the Rebetron than in the Pegasys plus Copegus arm.

Moving on to our protocol defined analyses. To orient the Committee to the left hand side, the comparison will be our primary comparison Pegasys plus Copegus versus Rebetron. On the right hand side, our secondary comparison, Pegasys plus Copegus versus Pegasys monotherapy.

You will note that our combined endpoints sustained virological response and sustained biochemical responses here at the bottom, 45 percent of patients randomized to Pegasys plus Copegus as compared to 39 percent of patients randomized to Rebetron achieved a combined endpoint with a P-value of 0.057 borderline statistical significance.

However, looking at the individual components of this definition we see that for sustained virological response, those randomized to Pegasys plus Copegus were 50 percent SVR as compared to 42 percent SBR for those randomized to Rebetron, a statistically significant difference.

Similarly for our sustained biochemical response, 50 percent of patients randomized to Pegasys plus Copegus as compared to 43 percent of those randomized to Rebetron achieved a sustained biochemical response, a statistically superior difference. If we look at the comparisons of Pegasys plus Copegus to Pegasys monotherapy, statistically significant, higher rates of response were seen in our combination arm, looking at sustained virological response, sustained biochemical response and the combined endpoint of SVR and SBR.

There has been an evolution in thinking and in endpoints since this study was developed which has been acknowledged in the FDA and the sponsor's briefing package. We now have a validated HCV RNA assay and virological response is considered the preferred efficacy endpoint.

Having presented our protocol defined analyses, I will now move on to focus on sustained virological response data and I want to point out the definition that we have as defined in our protocol. I mentioned it previously. Two negative HCV RNA

assessments, at least 21 days apart after week 60. It should be noted that there is an additional somewhat less conservative efficacy measure which is a single PCR determination. However, because we had focused on a two PCR definition in the protocol, we will be presenting that more conservative endpoint today.

Additionally, I will be presenting data using an all treated population, defined as patients randomized who have received at least one dose of HCV therapy.

Looking at the comparative trial versus Rebetron, you will note in terms of sustained virological responses that 52 percent of patients randomized to Pegasys plus Copegus as compared to 43 percent of those randomized to Rebetron achieved a sustained virological response which was a significant difference in superiority for Pegasys plus Copegus. Similarly, a higher SVR of 52 percent compared to 28 percent for Pegasys monotherapy, a statistically significant difference.

We were interested in assessing sustained virological response by genotype as has been outlined

in our protocol and you will see here the breakdown of sustained virological response for our genotype 1 patients as compared to our genotype non-1 patients. And for genotype 1 patients you will see the same pattern of response in terms of our three treatment arms. The highest sustained virological response achieved for Pegasys plus Copegus followed by a 35 percent virological response for Rebetron and a 19 percent virological response for Pegasys monotherapy. And with our genotype non-1 patients, again a similar pattern. The highest sustained virological response for Pegasys plus Copegus as compared to 57 percent for Rebetron and 44 percent for Pegasys monotherapy. There's been considerable interest in understanding the impact of high and low viral load within the genotype 1 population and we've performed some additional descriptive analyses of sustained virological response looking at our low and high viral load patients. And what I can say is that numerically, a similar pattern of response across the three arms have been observed for both our low viral load patients represented on the left and our high

viral load patients represented on the right.

The efficacy findings for this comparative trial versus Rebetron are therefore the Pegasys and Copegus sustained virological responses are superior to Rebetron as well as Pegasys monotherapy. This was seen in our overall population. It was seen in our genotype 1 population with contributions from both our high and low viral load patients and finally, it was observed in our genotype non-1 patients as well.

As Dr. Hoffman has mentioned, having confirmed the superiority of our Pegasys plus Copegus combination as compared to a non-pegylated interferon combination and to Pegasys monotherapy, we were interested in assessing the effect of dose and duration on patient subgroups with a particular emphasis on genotype. And as such, the second study NV15942 was conducted.

The primary efficacy objectives of this study were to compare the efficacy of Pegasys plus Copegus for 24 weeks versus 48 weeks. And secondarily, to compare the efficacy of Copegus 800 milligrams versus 1000 or 1200 milligrams in

combination with Pegasys. And the rationale for the doses selected have been outlined by Dr. Hoffman.

This study was also randomized. Treatment duration was blinded until week 24. Copegus dose was blinded throughout the study. This trial was stratified by genotype 1 versus non-1; by viral load, low versus high; as well as by geographic region. And patient selection criterion in terms of inclusions and exclusion criteria were the same as those that I've outlined in NV15801 or comparative trial versus Rebetron and I will not repeat them here.

Patients in this study were randomized to one of four treatment arms and I'll begin by saying that the Pegasys dose was the same throughout, that is, 180 micrograms subcutaneously given once a week. And the arm represented on the top of the slide, we see Pegasys plus Copegus in standard doses of 1000 or 1200 milligrams given for 48 weeks which is what we refer to as the common arm in that it was the same dose and duration as represented in the previous study.

The second arm is Pegasys plus Copegus,

but this time in a dose of 800 milligrams, also for 48 weeks.

The third arm is Pegasys plus Copegus in standard doses of 1000 or 1200 milligrams, administered for 24 weeks.

The fourth and final arm is Pegasys plus Copegus, 800 milligrams, also administered for 24 weeks. And in this study, patients were given 24 weeks of follow-up after the completion of treatment, before the determination of their efficacy endpoints.

The primary endpoint for this study was sustained virological response. Secondary endpoints included sustained biochemical response and the end of follow up histological response, again on a subset of 20 percent of patients randomized to the study. And the analysis population was all patients treated.

This slide represents the patient characteristics across the four arms. And I have a couple of points that I'd like to make in terms of genotype and viral load. The Committee will note that the proportion of patients randomized with genotype 1 to our 48 week treatment arms was higher than that

randomized to 24 weeks.

Similarly, patients with higher viral load essentially the genotype 1 high viral load patients were also preferentially enrolled to the 48 week arms. And this was the result of a pre-planned, unbalanced analysis which favored genotype 1 high viral load patients randomized to 48 weeks as compared to 24.

Other demographic characteristics that are known to have a potential impact on sustained virological response are listed here and are well balanced. I will point out that we have approximately 25 percent of patients with bridging fibrosis or cirrhosis, randomized to all four treatment arms of this study.

The mean age is approximately 42. The mean weight is approximately 77 kilos and the proportion of males is very similar to our comparative trial versus Rebetron, approximately 66 percent.

Again, briefly reviewing the reasons for premature withdrawal, Dr. Solsky will review our safety reasons. The total numbers of premature withdrawal are listed at the bottom of the slide. As

might be expected, patients randomized to receive a 48-week course of treatment as compared to a 24-week treatment course did have a somewhat higher rate of premature withdrawal. The primary drivers of this in terms of nonsafety are first of all, insufficient therapeutic response and again, we have the same rule that if a patient had not responded by week 24, they could be categorized as a nonresponder and leave study if they so choose. And also we had somewhat higher rates of refused treatment and failure to return in the two 48-week treatment arms as compared to the 24-week treatment arms.

As you will recall, our primary comparison for this study was treatment duration. An analysis of the data revealed that 48 weeks of treatment was superior to 24 weeks of treatment. In terms of our secondary comparison which was the Copegus dose, our analysis showed that 1000 or 1200 milligrams was statistically superior to 800 milligrams and this was an overall pooled analysis.

Looking further at impacts in terms of the patterns by genotype, we do note that for the genotype

1 patient population, 48 weeks was noted to be superior to 24 weeks and 1000 or 1200 milligrams appeared superior to 800 milligrams and we interpret this that the genotype 1 responses appear to be driving largely the overall pooled results that I have just shared with you.

Interestingly and importantly, however, in terms of our genotype non-1 patients, we were unable to detect a difference between 24 and 48 weeks of treatment and between 800 and 1000 or 1200 milligrams of Copegus.

And in order to further understand this we've proceeded in a predefined manner to explore descriptively the specific responses by genotype across the four treatment arms and I will review that data now.

Beginning with our genotype 1 patients, sustained virological response across the four treatment arms of the study, the Committee will note that the highest sustained virological responses were seen in the genotype 1 patients randomized to 48 weeks of treatment and 1000 or 1200 milligrams of Copegus.

There are lower point estimates, 39 percent, 41 percent and the lowest point estimate of 29 percent as we reduce Copegus dose or we reduce the exposure to treatment with the lowest genotype 1 response seen for patients randomized to receive only 24 weeks of treatment and 800 milligrams of Copegus.

A similar pattern of response was observed in both our high and low viral load patients. You will note a step-down from 48 weeks of treatment through 24 weeks of treatment for our genotype 1 high viral load patients, very similar to the overall genotype 1 group and again for our low viral load patients with a step down from 60 to 41 percent as we reduce dose and exposure.

A different pattern emerged with our genotype non-1 patients as may have been suggested by the pooled statistics that I shared with you. What we noted here was that high sustained virological responses were achieved when patients were randomized, non-1 patients to 24 weeks of treatment and 800 milligrams of Copegus and there was no increase apparent in terms of sustained virological response

with either an increase in Copegus dose or a doubling of treatment exposure.

Our efficacy findings therefore are that superiority of longer treatment duration and higher Copegus dose has been shown in our overall population and that for genotype 1 which we believe is essentially driving this effect, there is a consistent response with the overall. That is that the highest sustained virological responses are seen with 48 weeks of treatment and with Copegus 1000 or 1200 milligrams.

However, for genotype non-1 as has been suggested from some of the literature that Dr. Hoffman referred to, available with non-pegylated products, we see that high and maximal responses can be achieved with 24 weeks of treatment and lower doses of Copegus presenting a real opportunity to reduce exposure to both treatments without risking efficacy.

Moving on to predictability analyses, the objective of these exploratory analyses were to confirm predictability findings that we have seen from our monotherapy program and these findings were that if a patient had not achieved an early virological

response, response by week 12 which was defined as achieving at least a 2 log drop in HCV RNA or undetectability, there was a very low likelihood that this patient would proceed to sustained virological response with a negative predictive value in the range of 98 percent and this is actually represented in our labeling for monotherapy.

We were interested in validating these findings and seeing if similar predictability conclusions could be drawn with our combination data and for that reason we have performed this analysis on the Phase 3 patients who receive 48 weeks of treatment and 1000 or 1200 milligrams of Copegus from the two studies that I've just reviewed.

I've defined the early virological response, but I will recap it briefly. That is, that HCV RNA had to be reduced by greater than or equal to 2 logs or undetectability by week 12.

I'm going to focus this presentation on our genotype 1 findings although I will say that in this analysis our overall results are essentially the same. The reason for focusing on genotype 1 is that

we believe that this is the patient population where the ability to determine early virological response will be particularly helpful because these are patients who will require a full year of therapy for maximal efficacy.

Looking at the 569 patients who were genotype 1 included in this analysis, you will note that 82 percent did achieve an early virological response, but for this analysis the emphasis is on those who did not. The 18 percent or 102 patients who did not achieve an early virological response are represented on the low part of this figure. Of these patients only 4 or 4 percent went on to achieve a sustained virological response and 96 percent did not. So a negative predictive value can be calculated at 96 percent which is very similar to the numbers that we were seeing with monotherapy.

So we believe that this analysis certainly confirms what we had seen with monotherapy and it has been supported by our combination data and as I've mentioned this does allow for early decision making by patients and prescribers for those with a low

likelihood of achieving a sustained virological response.

In conclusion, the pivotal Phase 3 studies have demonstrated that Pegasys plus Copegus has achieved sustained virological responses that are superior to Rebetron as well as to Pegasys monotherapy; that for genotype 1, the highest sustained virological responses were achieved when Pegasys and Copegus were administered for 48 weeks and when the Copegus dose was retained as a standard dose of 1000 or 1200 milligrams according to a 75 kilo weight split.

However, for genotype non-1, maximal sustained virological responses were achieved -- can be achieved with Pegasys and with Copegus 800 milligrams used for 24 weeks without an apparent increase in benefit by moving to a full 48 weeks of therapy.

And with that I will close and ask Dr. Jonathan Solsky to join me at the podium to review the safety results from the two Phase 3 studies that I have just presented.

DR. SOLSKY: Good morning. The safety profile of the Pegasys-Copegus combination has been well characterized based on the two large, multicenter clinical trials that Dr. Duff has just presented which in total enrolled 1,735 HCV patients who received the Pegasys-Copegus combination and of which 377 at baseline had compensated cirrhosis or bridging fibrosis. Nodal scores F3, F4.

My safety presentation today will consist of two main parts: a safety comparison of the Pegasys combination versus Pegasys monotherapy and Rebetron based on our comparative trial NV15801 and then I will turn to a safety comparison of the Pegasys-Copegus combination by duration of treatment and Copegus dose based on duration and dosing by genotype study, NV15942.

This slide provides an overview of the safety profile of the Pegasys-Copegus combination in comparison to Pegasys monotherapy and Rebetron. In comparing the Pegasys-Copegus combination to Pegasys monotherapy one notes in both treatment groups, almost all patients reported one or more adverse events.

Serious adverse events including those assessed to be unrelated to therapy by the investigators were reported at the same rate of 12 percent in both groups.

There were two deaths reported on Pegasys monotherapy and none on the Pegasys-Copegus combination.

Dose modifications of Pegasys were reported at a rate of 27 percent on Pegasys monotherapy and 32 percent on the Pegasys-Copegus combination and this was attributable more due to adverse events and neutropenia. Furthermore, dose modifications of ribavirin were noted at a rate of 40 percent on the Pegasys-Copegus combination and this was attributable to both adverse events and anemia.

In terms of premature withdrawals, 7 percent were reported on the Pegasys monotherapy and 10 percent were reported on the Pegasys-Copegus combination.

Turning to a comparison of the Pegasys-Copegus combination in relation to Rebetron, one notes once again that in both treatment groups

almost all patients reported one or more adverse events.

In terms of serious adverse events, including those that were considered to be unrelated to therapy as assessed by the investigators, on the Pegasys-Copegus combination, it was noted at a rate of 12 percent in comparison to 9 percent on Rebetron. Looking at these serious adverse events that were considered to be treatment related to therapy, there was a similar rate of 4 percent in both groups.

There was one death that was reported on Rebetron and in terms of dose modification of note is that dose modification of Pegasys occurred on 32 percent on the combination in comparison to 18 percent on Rebetron. This was mainly attributable due to neutropenia and thrombocytopenia.

In terms of dose modifications of ribavirin this was noted to be at a similar rate of 40 percent on the Pegasys-Copegus combination versus 37 percent on Rebetron.

Finally, in terms of premature withdrawals in both treatment groups, they were reported at the

same rates. This last finding suggests that dose modification for laboratory abnormalities in most cases are effectively managed by dose modification and rarely were these laboratory abnormalities treatment limiting.

The follow slides I will now go through will go in further detail regarding each of these particular safety parameters I have just touched upon in my overview.

First, turning to the most common adverse events reported in this trial, overall, in all three treatment groups, the overall incidence was reported at a comparable rate. Of note, in comparing the Pegasys-Copegus combination to Pegasys monotherapy, there were differences in point estimates between the two groups. With the addition of ribavirin to Pegasys one notes that there was a difference in terms of fatigue, insomnia, appetite decreased and dermatitis.

In comparing the Pegasys-Copegus combination to Rebetron, again one noted point estimate differences in terms of flu-like symptoms such as pyrexia, myalgia, rigors as well as

depression.

Turning to serious adverse events in all three treatment groups, serious adverse events were reported infrequently. In addition, on looking at unusual or unexpected adverse events, none were reported on the Pegasys-Copegus combination that have not been previously reported with interferon therapy in general. Furthermore, when we group these particular adverse events under their respective body systems, we noted that the most common adverse events included infections, gastrointestinal disorders and neuropsychiatric disorders. Since infections and depression are two areas of major concern with interferon therapy, we looked at both of these areas in greater detail and I would like to present this information to you.

First, in terms of patients with infections, you'll note that there was a report of all infections reported at a rate of 40 percent on Pegasys monotherapy; 46 percent on Pegasys-Copegus combination; and 35 percent on Rebetron. In terms of the most common causes for these particular infections

they included sinusitis, upper respiratory tract infections, tooth abscess, herpes simplex, bronchitis and influenza. We then did a very thorough and comprehensive review of all serious adverse events that were reported in our data base to see if they had an infectious etiology. We looked to see whether a pathogen was isolated or that patients were treated with antibiotics and in so doing identified 7 cases on Pegasys monotherapy, 16 cases on the Pegasys-Copegus combination and 18 cases on Rebetron.

On further review of the 16 cases on the Pegasys-Copegus combination, we noted no predominance of any particular type of infection or involved organ system or particular type of pathogen. In those cases where a pathogen was isolated, the most common pathogens included staph aureus, strep pneumonia and e.coli.

We looked at the time to onset of these infections from the initiation of therapy and as you can see here these infections occurred throughout the course of the study itself. We noted that there was no correlation of infection with a preceding rate for

neutropenia. It's important to note that in many of these cases, the patients were hospitalized for these serious infections and therefore the emitting hospital labs were not entered into our data base. And so in order to do another analysis of this information, we looked at a time window around the infection and their lowest ANC and in so doing we have summarized these findings here. The majority of these cases of infection had absolute neutrophil counts of greater than 1500 and there was only one case where the patient had an ANC of less than 500 around the time period of infection. In this particular case, it was a situation of an Oxacillin resistant staph aureus epiglottitis that occurred. At the time of the symptomatology first presenting, the person had an PMN of 1600 and during the next two weeks both the patient's PMN and platelet counts continue to drop prior to them being hospitalized and antibiotic therapy being initiated.

There were 3 of the 16 patients who were withdrawn from therapy and the remaining 13 were able to be effectively treated with antibiotics, the events

resolved and the patients continued on therapy. I should also note that none of these 16 cases required GCSF.

Turning to depression, depression was reported at a rate of 20 percent on Pegasys monotherapy; 22 percent on the Pegasys-Copegus combination; and 30 percent on Rebetron. In terms of serious depression necessitating hospitalization, there were no cases on Pegasys monotherapy, two cases on the Pegasys-Copegus combination and seven cases on Rebetron.

In terms of treatment for the depression, 11 percent were reported on Pegasys monotherapy; 14 on the Pegasys-Copegus combination; and 21 percent on Rebetron.

In terms of dose modification, this was, as you can see, rarely done in these treatment groups. And were similar.

Suicidal ideation and suicide attempt were reported relatively infrequently within these groups and at a somewhat similar rate and premature withdrawals were no different in terms of Pegasys,

Copegus and Rebetron and was reported at a lower rate on Pegasys monotherapy.

Turning to the deaths that were reported in this trial, there was in total three deaths that occurred; two on Pegasys monotherapy; one on Rebetron and as I indicated there were none on the Pegasys-Copegus combination. All three of these deaths were considered to be unrelated to therapy and all of them were reported after the discontinuation of therapy.

Turning to dose modification, as I had mentioned in terms of the overview, one notes a higher rate of dose modification of 32 percent on the Pegasys-Copegus combination in comparison to 18 percent on Rebetron. As you can see, this difference is not attributable due to a dose modification for adverse events since these were reported at the same rate in both treatment arms, but rather due to laboratory abnormalities, specifically neutropenia and to a lesser extent thrombocytopenia.

Turning to dose modifications for the ribavirin component of these two combinations, one

notes a similar reported rate of 40 percent on Pegasys-Copegus versus 37 percent on Rebetron. The slight difference that is noted is attributable due to anemia.

Turning to laboratory abnormalities, since we had noted this increased rate of modification on the Pegasys-Copegus combination, we wanted to better understand how these laboratory abnormalities were managed.

This slide summarizes patients who had the lowest neutrophil count, grade 4, defined as a neutrophil count of less than 500 cells per ml during the course of study. Grade 4 neutropenia was reported in 8 cases on Pegasys monotherapy, 21 cases on the Pegasys-Copegus combination; and 5 cases on Rebetron.

Looking at specifically how these events were managed, in terms of dose modification whether it be permanent, temporary or not even done one notes of the 21 cases that occurred on the Pegasys-Copegus combination, 18 of these were managed by dose modification and only 3 of them necessitated treatment withdrawal. This finding is also seen on Pegasys

monotherapy, where of the 8 cases of Grade 4 neutropenia all 8 were able to be managed by dose modification and none required treatment withdrawal.

Turning to thrombocytopenia, there were no cases of Grade 4 thrombocytopenia defined as a platelet count of less than 20,000. In terms of Grade 3 thrombocytopenia, defined as a platelet count between 20,000 to 50,000, one notes that there were 14 cases reported on Pegasys monotherapy; 22 cases on the Pegasys-Copegus combination; and 1 case on Rebetron. Similar to what we saw with neutropenia, the majority of the cases, 18 out of the 22 were able to be managed by dose modification and only 4 necessitated treatment withdrawal. This was also seen in Pegasys monotherapy, where 13 of the 14 cases were able to be managed by dose modification and only 1 required treatment withdrawal.

Turning to patients with a hemoglobin of less than 10 grams were deciliter that was reported during the conduct of the study, one notes that there were 8 cases on Pegasys monotherapy and a similar number on both the Pegasys-Copegus combination and

Rebetron, with a reported rate of 11 percent in both treatment groups. Again, similar to what we have shown previously, the majority of these cases of anemia could be managed by dose modification and a few patients necessitated withdrawal of treatment for this lab abnormality.

Turning to premature withdrawals, as I had indicated previously, there was no difference between the two treatment groups of Pegasys-Copegus and Rebetron in terms of withdrawal. In terms of the most common cause for treatment withdrawal, this was psychiatric events which were reported at 3 percent on the Pegasys-Copegus combination versus 4 percent on Rebetron.

In terms of blood disorders, specifically the neutropenia, thrombocytopenia, anemia, there were 7 cases reported on the Pegasys-Copegus combination in comparison to 3 on Rebetron.

In terms of other reasons for premature withdrawal defined by body system, as you can see all of these were reported at less than 1 percent for the Pegasys-Copegus combination.

I'd like now to turn to our duration and dosing by genotype study, NV15942, and provide a safety comparison of the Pegasys-Copegus combination by duration of treatment and Copegus dose.

This slide provides an overview of the safety profile of the four treatment groups. In terms of the common arm that was studied in both the previous study as well as this, the safety profile that one sees here is similar and consistent to that which we had reported in our 801 comparative trial.

In terms of further benefits of reducing both the duration and dose of Copegus, one notes that there was a reduction in the rate of serious adverse events, dose modifications for both Pegasys as well as more so for Copegus, as well as also in terms of premature withdrawals.

Looking at serious adverse events, although based on body system there was a relatively small number of cases in any particular body system of a serious adverse event, nonetheless, one sees a consistent trend of a reduction of these serious adverse events as one reduces both the duration and

dose of treatments.

This is also seen in terms of patients with a hemoglobin of less than 10 grams per deciliter and as one reduces both the dose of Copegus as well as the duration of treatment, one notes this reduction in rates. Furthermore, and as has been seen in the data I've just presented from our comparative trial, one sees that the majority of the cases were able to be managed by dose modification and few patients necessitated treatment withdrawal.

In terms of deaths that were reported in this trial, there were a total of four. Two of these were considered to be unrelated to therapy and two were considered to be related to therapy. The first three cases, the heroin overdose, case of septicemia and suicide, all were reported while the patients were receiving drug and the fourth case of polysubstance overdose was reported approximately four and a half months after the completion of therapy.

Ribavirin is a known teratogen and as such is a major concern both during the conduct of the study itself and for six months after the completion

of the study, given the pharmacokinetics of ribavirin. In our two pivotal trials that we've just discussed, we had 10 cases of pregnancy reported in these trials. Three of these occurred in female patients and seven in female partners of male patients, the latter is of concern as ribavirin is distributed into the sperm. In terms of pregnancy outcome, one notes that there were three elective abortions; five normal births; one premature birth that occurred in a female partner at 25 weeks gestation. This was a child that had a normal appearance, unfortunately four days after the birth, the child died of a pulmonary hemorrhage. Both the obstetrician and the treating physician had indicated that they did not feel that this was related to the ribavirin. And there was one case that the patient was lost to follow-up.

While these overall pregnancy outcomes are not remarkable in comparison to the general population, nonetheless, this is an area of major concern to Roche and as such, we intend to implement a Copegus pregnancy risk management program. The elements of this program are summarized on the

following slide.

We will be obviously having detailed information regarding pregnancy risk and teratogenicity that will be labeled within the package insert and this will also be reflected in the patient medication guide.

Furthermore, we intend to provide educational brochures to both patients as well as female partners to better understand the risk of pregnancy when taking this therapy and also to have understanding regarding effective contraceptive use.

We will also be providing similar information to health care providers and physicians regarding this type of information.

In addition, should a pregnancy develop in patients, we are implemented a pregnancy registry where we will systematically collect information on these pregnancies and follow up the patients in terms of evaluating their outcomes.

I'd like to now conclude by summarizing the safety findings from these two trials. The clinical safety profile of the Pegasys-Copegus

combination is comparable to Rebetron. While there was a higher incidence of laboratory abnormalities, specifically neutropenia and to a lesser extent thrombocytopenia with the Pegasys-Copegus combination in comparison to Rebetron, these events were clinically manageable by dose modification in most cases. And the incidence of discontinuation for safety reasons was the same between the Pegasys-Copegus combination and Rebetron.

Furthermore, in the appropriate HCV population, a shorter duration of the Pegasys-Copegus combination and a lower dose will provide fewer serious adverse events, fewer cases of anemia, fewer dose modifications and fewer premature withdrawals.

I'd like to now turn the mic over to my colleague, Dr. Hoffman, who will give some concluding remarks regarding benefit risk.

Thank you for your attention.

DR. HOFFMAN: Just very briefly before wrapping up our presentation, I wanted to point out that we have a number of on-going studies. I've told you something about the monotherapy program and you've

heard now about the combination therapy program. We have a third registration program of two Phase 3 trials which will be concluding in the next year or so, a trial in HCV/HIV coinfection and also a trial in patients with normal ALT. Patients with normal ALT make up perhaps as many as one third of the patients with chronic hepatitis C.

Other on-going efforts that we have outside of registration program include African American patients, cirrhotic patients, the HALTC trial that you may be familiar with, pediatric patients, patients with previous liver transplants, methadone users, nonresponders to previous interferon-based therapies. We're also looking at Pegasys in combination with new therapies as well as other indications, hepatitis B and oncology.

First, what is the impact of adding ribavirin to Pegasys? As demonstrated in the 801 comparative trial, the superior efficacy demonstrated from the combination of Pegasys and Copegus as opposed to Pegasys monotherapy in the overall population as well as in patients with genotype 1 and genotype

non-1.

The safety profile is similar between the combination of monotherapy with the exception of anemia due to the addition of the ribavirin component.

What about looking the combination of Pegasys and Copegus versus Rebetron. Again, superior efficacy demonstrated in the overall population and also by genotype. In genotype 1, the statistical improvement was contributed to both by the low viral load and high viral load patients and in also in genotype non-1.

Overall, a similar safety profile, although as Dr. Solsky mentioned, there was an increase in neutropenia, thrombocytopenia and infections in the Pegasys-Copegus arm. These rarely resulted in premature withdrawal and are treatable with dose modification and there was a lower incidence of depression and certain flu-like symptoms in the Pegasys combination arm.

The second study added some additional information and that is in genotype 1, the highest efficacy was demonstrated with the full dose of

Copegus 1000 or 1200 milligrams given for the full duration of 48 weeks. However, for genotype 2,3 not only could the duration be decreased to 24 weeks without apparent loss of efficacy, but also the Copegus dose from 1000 to 1200 down to 800. And this was associated with a significant safety savings.

Now in both this trial and the first trial, we demonstrated that using a combination of quantitative and qualitative measures, HCV RNA, nonresponders could be identified for the most part at week 12.

So in conclusion, the combination of Pegasys and Copegus represents an improvement in the treatment of chronic hepatitis C, both over Pegasys monotherapy and over Rebetron. Importantly, treatment can be tailored according to genotype to optimize benefit risk relationships. Genotype 1 patients do best with full dose of Copegus for a full duration. However, the use of the week 12 predictability can be used to increase benefit risk due to the fact that patients may be adequately treated with 24 weeks of therapy with a lower dose of 800 milligrams of daily

Copegus.

This concludes the sponsors presentation. Thank you.

DR. GULICK: Thanks very much, Drs. Teuber, Duff, Solsky and Hoffman.

We're going to hold questions from the Committee until after the Agency presentation.

We're due for a break right now and we will reconvene at 10:15.

(Off the record.)

DR. GULICK: We'll reconvene. Dr. Stanley, can you hear me?

I'm not sure whether that was a yes or not.

Can you hear me, Sharilyn?

DR. STANLEY: I'm here.

DR. GULICK: Okay. We can hear you.

(Laughter.)

DR. STANLEY: Oh good.

DR. GULICK: We turned you down, so you're fine.

DR. STANLEY: Thank you.

DR. GULICK: Okay, we'll turn now to the Agency's presentation by Dr. William Tauber.

DR. TAUBER: Members of the Advisory Committee, ladies and gentlemen, good morning.

I may need some technical assistance here.

(Pause.)

You'll have to forgive my technical inexperience here. In the next hour, we will consider the FDA perspective on the efficacy and safety of Pegasys Copegus. The FDA presentation has two objectives. The first objective is to confirm the sponsor's analyses and interpretation of key clinical data. The second objective is to identify and explain differences between the Agency and the sponsor in the interpretation of some of the safety and efficacy data.

In general, these differences are in areas where clinical data are too few or inconclusive to provide definitive answers. We will be asking the Committee to discuss and provide advice on these issues.

Next slide. This is the first --

actually, the second slide and its intention is to basically draw to focus the purpose of our meeting. The indications and usage of Pegasys and Copegus in combination are indicated for the treatment of previously untreated patients with chronic hepatitis C infection. This is to highlight the fact that this Roche's pegylated interferon product and Roche's ribavirin product.

Moving on to a very brief review of some of the data already discussed by Dr. Hoffman, on the treatment of hepatitis C, interferon alpha-2a monotherapy enjoys a success rate of around 15 percent. Pegylated interferon alpha-2a monotherapy in the recently approved product demonstrated a sustained virological response of 30 percent. Interferon alpha-2a with ribavirin has a sustained virological response of 45 percent and pegylated interferon alpha-2b when used in combination with ribavirin in an approved product that's currently available has a sustained virological response in the 50 percent range.

There are worthwhile factors that again I

would like to repeat. I know they've been brought up earlier and that is there are factors that we know influence a patient's response to alpha interferon treatment. These factors include HCV genotype and viral load, cirrhosis, advanced or older age and as you see race is listed as an adverse risk and by this we mean that it has been demonstrated that in African American populations the response rate to alpha interferons has not had the same level as was found in the non-minority population.

The next slide, the study drugs and this may seem repetitious, but its point is to make certain that with all the As and Bs that we keep them all straight.

Hoffman-LaRoche and Schering Plough produced products that are part of the study conduct in this application. This is not meant to be an exhaustive cataloging of all the alpha interferons that are available, but simply those that are found in this particular application.

Hoffman-LaRoche makes interferon alpha-2a or Roferon A. It also makes a pegylated interferon

alfa-2a and that is Pegasys and for the purposes of this application, they have produced a ribavirin called Copegus in a table form as opposed to the capsule form produced by Schering Plough.

Schering Plough has -- their contribution to this study includes interferon alpha-2b, ribavirin that is called Rebetol and interferon alpha-2b and ribavirin combination or Rebetron.

Dr. Hoffman did an excellent job of reviewing the clinical development so I won't spend much time on this, but I would like to briefly review that the Phase I studies were in monotherapy and they looked at the pharmacokinetics of Pegasys and they looked for the comparability issues between Copegus and Rebetol. The Phase 2 study which Dr. Hoffman did allude to represented a rather small study of 20 patients. Its goal was to examine safety of the combination as well as to gather pharmacokinetic data in particular the effect of food on ribavirin absorption.

Next. The Phase 3 clinical development, as was mentioned earlier, there were two pivotal

studies; 15801 which was randomized partially blinded study, comparing Pegasys Copegus to Rebetron. It enrolled 1121 patients as will be discussed.

Study 15942 was also randomized, double blinded and in this case treatment duration was examined to see whether a 12 or 6-month course of therapy would be superior and it was also designed to examine whether a reduced dose of ribavirin would be equivalent or roughly equivalent to the higher dose.

Some time was spent by Dr. Hoffman regarding the rationale for selection of the peg-interferon and ribavirin dosages and I'd like to just review those briefly. There were three monotherapy studies which I'm not going to spend much time on. I would like to -- I have neglected to mention the Phase 2 study that we talked about, the 15800. There was no dose ranging that was performed for the combination within the context of that study.

The rationale for the selection for the ribavirin dose, again the similarity of PK data of Roche's and Schering's ribavirin and whoops -- we're getting ahead of ourselves. The 1000 to 1200

milligrams is the recommended dosage for the approved product Rebetol and formed a reasonable basis for a study in using this Roche ribavirin product. And 800 milligrams, it should be pointed out, is the recommended dosage for Schering's ribavirin and peg-interferon alpha-2b combination. So it again made a logical step to use that -- select that dosage.

I'd like now to move to the analysis of Phase 3 clinical trials. I'm not going to dwell on the inclusion and exclusion criteria. Dr. Hoffman demonstrated those very well. I would like to point out that this was very much an international study. There were involvement of North and South America, Europe, Asia, New Zealand and Oceania. U.S. patients made up 37 percent of the total patient enrollment for the study, for both studies, excuse me.

The assessment of response in both studies and now what I'd like to do is talk about what these two shared in common. They both started with a primary endpoint at 24 week post-therapy of a combined sustained virological response and sustained biochemical response. In Study 2, this was amended

during the conduct of the study to sustained virological response alone. Both studies had futility withdrawal at 24 weeks. And this was very well described and I always seem to get it backwards whether it's positive or negative, but those individuals who did not meet the criteria for early virologic response were to be discharged at 24 weeks time unless they had evidence of a sustain biochemical response, that being that they had a normalization of their ALT. So yes, it is true that there were individuals who were retained with a sustained virological response not achieved, who were continued on therapy because they had met the sustained biochemical response.

Let's go ahead and look at the particulars of the study, 15801, Study 1. The study design, as was very well discussed, enrolled 1121 patients. They were randomized as was cited, 1 to 2 to 2. I'm taking the monotherapy first. The dosing was Pegasys 180 micrograms, subcu, 2 week; Intron A was given at 3 million international units, 3 times a week; and ribavirin was given 1000 to 1200 milligrams in the

formula previously mentioned of the 75 kilogram breakpoint. The respective ribavirins were given to the respective interferons.

The primary efficacy analysis for this study was the intention of treating population which was defined as all randomized. The Cochran-Mantel-Haenszel test with stratification variables of country and genotype were employed. The primary comparator arms here were the Pegasys Copegus and the Rebetron.

I'd like to discuss the demographics of this population. As was shown earlier, they were very well matched, balanced across the study arms. The population was predominantly white male with a median age of 42 to 43 and the median weight was 79 kilograms.

As you look at this slide, you notice that I have broken down the demographics a little bit and I have the U.S. versus the non-U.S. population listed here and there's a purpose for that. The first of these being that although the gender and race attributes are the same between the two divisions,

U.S. versus non-U.S., when you look at those patients over the age of 44 and I guess it's difficult to call that elderly, but those over 44, I chose the median point of U.S. population versus non-U.S. and you'll see that half of the American patients or U.S. patients were over 44 years old as opposed to 35 percent of the non-U.S. and I know only too well weight was a bigger factor in U.S. patients than it was in non-U.S. patients.

What about the baseline disease characteristics? As was mentioned earlier, we know that high viral load, genotype 1 and cirrhosis are all adverse factors. Well, how did that work in terms of the U.S. versus the non-U.S.? Well, the U.S. had a little bit more of everything: 68 percent of the high viral load, 70 percent of the U.S. patients had genotype 1 and cirrhosis was found 16 percent versus 11 percent.

Well, that's who was enrolled. What happened to them? This is the primary advocacy outcome, you've already seen and this is the combined response that we spoke of, that was spoken of earlier.

And there's a 6 percent difference between these two values and the P-value is 0.057.

If the primary efficacy analysis is examined as the sustained virological response, the numbers are a bit different with 50 percent versus 42 and at this point the P-value is now 0.01.

What about subgroups? Obviously, at this point we're looking at more descriptive analyses since we've already moved beyond the primary statistical analysis.

This is the all treated population and you see that again the delta between the Pegasys Copegus and the Rebetron is now 9 percent. The striking thing about this -- there are a couple of things that I'd like to bring to your attention about this particular slide. First of all, the delta was positive in all the categories with the one exception being in black patients versus white patients. And the reason for this is that the numbers are so -- perhaps are so small that we cannot determine the meaning of this data. There's 40 individuals involved in the two arms.

Another thing that I'd like to point out and the standard things that we would have expected occurred. Patients with cirrhosis did less well than patients without cirrhosis. Patients that were younger did better than patients who were older. And the other thing I wanted to point out is perhaps a little bit unexpectedly, but maybe not, the U.S. patients, although the same difference with the superiority of Pegasys Copegus existed, you'll notice that the difference between within the arm, between U.S. and non-U.S. patients is considerable in both arms. This was not just Pegasys Copegus, but Rebetron also demonstrated this very same phenomenon.

What about histologic responders? This has obviously been a very important issue that has been addressed in the past and I wanted to touch on it today.

The first point I wanted to make is that only a small fraction of the total population had a liver biopsy. We're talking about there were 198 patients that actually underwent impaired liver biopsy. There were approximately 285 that had been

originally planned.

When you look at the results, the results are somewhat similar across all three study arms. You see that from a low of 72 percent up to a high of 80 percent. There still is, regardless of treatment, a large number of responders in both groups. You might ask what is the type of response that you see and it's predominantly inflammatory. For those that are responders, the majority were individuals that showed improvement in inflammatory scores. The HAI scores, you all recall, is a compilation of four factors with a numerical score assigned and the fourth factor being fibrosis and the other three being inflammatory.

If you look at fibrosis alone, of these responders, the only -- about 31 individuals out of 198 actually showed improvement in their fibrosis scores.

Well, what about sustained virological response by genotype and region? We've talked about the region. We've seen some things, what does it look like when we compare it graphically?

Genotype 1, you'll notice -- to orient

you, the first -- the red, I'm sorry, the red and the orange are somewhat similar, but the red is the Pegasys Copegus SVR in the U.S. The green is the Rebetron in the U.S. The blue is the Pegasys in the non-U.S. and the orange is the Rebetron in the non-U.S.

And what you see -- what we were talking about earlier is that in each case this bar is taller than this bar except perhaps this one here, but the blue bars are, as you see, invariably taller than the red bars which again is graphic evidence that there is a difference between the two populations in terms of sustained virological response.

If we take away the region, then this all becomes a lot simpler and the red bar which is the Pegasys is uniformly superior in all categories, genotype 1, genotype non-1, high viral titer and low rival titer.

Well, here's my favorite. Body weight. Does it make a difference? Well, actually it does. If you choose 85 kilograms, that's the 50 percent mark for the U.S. population, you find that the red bars

which are those individuals that are under 85 kilograms appeared to have a better efficacy than those individuals who were greater than 85 kilograms.

I'd like to move to adverse events. I would like to point out that as was pointed out by Dr. Solsky, that the severe adverse events were fairly well matched across all three study arms. The serious adverse events were as you see them 12 percent in the two Pegasys containing arms versus 9 percent in the Rebetron arm. I have the deaths percentages, but they're the same numbers that Dr. Solsky presented.

Withdrawals between the two comparator arms are very similar, at 10 percent, 11 percent. I'd like to stress, however, the difference between the dose modification and point out that Pegasys had a 32 percent increase and Rebetron, an 18 percent. The two ribavirin containing arms had very similar adverse events.

How about serious adverse events? Serious adverse events were numerically higher in the study arms containing Pegasys, either as monotherapy or in combination with Copegus than they were in the

Rebetron arm. If we combined neuro-psychiatric because it's sometimes difficult to tease these apart, patients with insomnia and with difficulty concentrating it may be we we're talking about depression or maybe it's a neurologic, but what is seen that there's pretty much a constant value across. There's not a large difference between the three study arms.

Infection, I guess it depends on how you round it. The sponsor has 4 percent for infection. I have 3 percent. It's really 3.4. I guess we'll just have to go with that.

Gastrointestinal adverse events, serious adverse events were more common in those individuals that were receiving ribavirin.

How about number of serious infections? Well, the incidence of serious infections was numerically twice as high in the Pegasys arm. Actually, in both Pegasys arms than it was in the Rebetron arm, although the difference is more marked in the Pegasys Copegus than it is in the Pegasys monotherapy. Most of the infections, although there

wasn't a predominant organism, there was a predominant type. These were bacteria and not only were they bacteria, they were bacteria that were members of a patient's normal flora.

There was severe neutropenia and leukocytopenia, occasionally documented in proximity to the infections and it's unknown exactly what the contribution of the neutropenia and leukocytopenia might have been, if any.

Next slide. Neutropenia was very common. As was stated earlier, Grade 4 occurred 5 percent of the time, but there is a great deal of neutropenia. Very few patients did not develop neutropenia while on study.

I'd like to point out there are two curves here. There's a blue curve and there's a green curve and the green curve being the Pegasys Copegus is shifted to the Grade 3 neutropenia. The blue curve seems to peak at the Grade 2 or 500 points higher. And you could argue well, okay, so, but obviously this would be a less desirable outcome for the clinician.

What about lymphocytopenia.

Lymphocytopenia was also very common, but unlike neutropenia it appeared to be fairly balanced across all three study arms with the exception that it appears the monotherapy and there's a -- the way this is presented, gives you the feeling as if there was a lot more problems with the monotherapy, and that's just because there were very few monotherapy that continued to go on.

What I'd like to point out here is that lymphopenia was more common, appeared to be more common, more severe in the ribavirin containing arms. Again, the role for ribavirin in terms of lymphopenia is not known.

What about patient withdrawal numbers? As was pointed out earlier by Dr. Solsky, the numbers are very similar, 11 percent in the Rebetron and 10 percent in the Pegasys arm. Adverse events were again fairly well matched and there was a tendency or trend toward increased psychiatric discharges in the Rebetron -- withdrawals compared to the Pegasys arm.

Laboratory abnormalities were patients were seldom withdrawn for laboratory abnormalities and

they were fairly well matched between the two comparator arms.

What about dose modifications? Well, dose modifications were mostly done for laboratory abnormalities. In this slide, just to orient you again, this goes with this and this goes with that, but I put them side by side so you can see a head to head competition or comparison, better word, between the two interferons and the two ribavirins. The things to point out here is that most common reason for dose modification in the interferon components was neutropenia and thrombocytopenia. That being said, Pegasys appeared to have a higher incidence. These are percentages now, a higher incidence of neutropenia than did the Intron A. Thrombocytopenia, likewise, was more common in the Pegasys than in the Intron A.

I wanted to talk about serum triglyceride briefly. It has been reported in the literature that serum triglycerides do -- are elevated during interferon treatment and that was found in this study. And it looks as if most of the three study arms are fairly well matched. The difficulty with interpreting

this data, however, is that these are random triglyceride levels and it is uncertain what the values would be if they were consistently drawn on a fasting -- in a fasting state.

What about laboratory abnormalities by weight? We evaluated the potential influence of body weight on safety profile of interferon alpha-2a ribavirin. The incidence of anemia and that's a hemoglobin less than 10 and to orient you, I selected 65 kilograms and what you'll see that in the monotherapy, there seems to be a slight increase between the under 65 and over or greater than or equal to 65, but in the ribavirin arms that difference is accentuated.

When you look at neutropenia, there is in the nonribavirin containing arms, very little difference between the 65 kilogram and above 65. However, in the Pegasys Copegus group, there is not only is there overall a higher degree of neutropenia, but there is a little bit more of a difference between them, again potentially asking a question about ribavirin.

Well, maybe it isn't just weight. Maybe it has to do with obesity or not obesity. That sounds like a question. If you look at BMI of 25 as being the breakpoint between when a patient is determined to be obese or not and you ask the same question we did with the 65 kilograms, what you find is and that again this seems to hold some merit in that the bar, the under 25, this appears to be taller, ever so slightly than the -- than its companion bar, so maybe obesity has some protective value here. And in neutropenia, again separating them out, the difference is small, but it certainly is consistent.

Summary. The first point I want to make is that Pegasys, 180 micrograms subcu Q week, combined with Copegus 1000 to 1200 milligrams per day in divided doses has a higher sustained virological response than does Intron A with Rebetol, Intron A at 3 million International Units three times a week and the Rebetol being 1000, 1200 similarly dosed.

The treatment difference again using the sustained virological response is 8 percent. Prognostic factors associated with lower response

include hepatitis C virus, genotype 1; high viral titer, that being defined as those greater than 2 million copies per milliliter; cirrhosis, older age, higher body weight, which we've added to the list; and response rates are lower in the U.S. compared to the non-U.S.

What about safety? Pegasys Copegus had higher observed incidence of certain adverse events compared to Rebetron. Serious adverse events were numerically higher, 12 percent versus 9 percent. Serious infections were 3.4 percent versus 1.7 percent. Grade 4 neutropenia was 5 percent versus 1 percent. Grade 3 thrombocytopenia was also 5 percent versus 0.2 percent. Dose modifications were required or used in 32 percent versus 18 percent. Both products had similar premature withdrawals and there was greater toxicity perhaps with lower body weight.

Moving on to the second study, 15942. The clinical protocol which has already been gone over, there was 1311 patients who were randomized by genotype, viral load to four arms receiving the same dose of Pegasys, 180 micrograms, subcu per week. The

two treatment arms were 24 weeks versus 48 weeks. The two ribavirin dose arms were 800 milligrams of fixed dose and 1200 milligrams, again weight adjusted, crudely at the 75 kilogram level.

The primary efficacy analysis was a sustained virological response and the intention to treat population which in this instance was defined as all randomized patients who had received at least 1 dose of study medication.

The Cochran-Mantel-Haenszel test with stratification variables of region; HCV genotype and titer and ribavirin dose were utilized.

I place this slide because as was mentioned earlier, this was an unequal allocation study. It was reasoned that the individuals with the genotype 1 high viral load were the most difficult to treat and they were categorized as such and it was basically felt that the other three, including genotype 1 low viral load might behave more in common with genotype non-1 than it did with genotype 1 high viral load. Therefore, the allocation and this is the actual numbers. There were some modification during

the conduct of the trial and these are the actual proportions that resulted at the end.

There were 1 to 1 to 4 to 4 of the genotype 1 high viral load and all the other three arms, the three strata, excuse me, were allocated alike, it was originally 1 to 2, so when it was changed from 1 to 1 to 1, we got a value in between of 1.5 in the higher ribavirin dosages than in the lower ribavirin dosages.

The primary objective as was stated earlier of this trial was to prove the superiority of 48 week treatment versus 24 week and also to examine whether 800 milligrams of ribavirin was equivalent to 1000/1200 in terms of efficacy.

Here are the population characteristics of this population. Again, I'll point out the same things that are different and that is that Americans are older in this and they're heavier.

What about baseline disease characteristics? The high titer were relatively equally matched between the two populations. As was stated earlier, the genotype 1 because of the nature

of the study which was to look at the non-1 population, the overall percentages are 58 percent versus the 65 percent in the first study. So there are more genotype 1 in this study.

Cirrhosis was more prevalent in this study at 25 percent. U.S. population had 29 percent. The non-U.S., 23 percent. And genotype 1 was 61 percent versus as you can see 56.

The way to present this data, because it is important to stress that all four arms of the study are not comparable in the same way because they have different patient populations because of the unequal allocation. Therefore, you can't take a sustained virological response from arm 1 and directly compare it arm 3 and have a meaningful analysis.

Therefore, we're looking at the pooled analysis, comparing 48 weeks with 24 and 1000/1200 with 800. The odds ratio favoring the 48 week was 1.32 and this is the interval. P-value was 0.039. How about the ribavirin dose? Again, the odds ratio was 1.5 favoring the higher dose for the total population and the P-value was 0.018.

At this point we leave the statistically significant area of the analysis and look at the descriptive. What about the percent sustained virological response by strata? I'm afraid the strata have gone through the ceiling. Treatment duration and ribavirin dose.

What you see here again using the same pooled format is that the 48 week for the genotype 1 high viral load appears to be higher than the 24 week and the 1000 -- there's a 1200 milligram there also. Also, appears to be higher than its companion fixed 800 milligram.

If you look at the 3 strata, there were felt to be low, lower difficulty in treating, you find that in genotype 1 again, the same number trends are there, 57 versus 47 and 56 versus 47. And when you get to the non-1s, it seems as though there's very little difference between the 48 week versus the 24 and 1000/1200 versus 800.

What about how would this look if it was presented graphically and what you see here, again, and what's shown earlier in a different slide by the

sponsor is that the genotype 1, there seems to be a fairly steady step-wise increase as you start from the 24 week Pegasys with 800 milligram to 24 week all the way up to the Pegasys 1000/1200 milligrams at 48 weeks. And you see graphically the differences are much less in the non-1 and almost the same slide, a different technique, the genotype 1 low with again, the 48 week being preferable with the high dose being with the genotype 1 even in the low titer appeared to be more successful.

Now this is a bit contrary to the hypothesis of the study which was the genotype 1 low viral load would behave in a different way.

What about sustained virological response by body weight. Again, the people that were under 85 kilograms appeared to have a higher level of sustained virological response than those above 85 kilograms.

What about cirrhotics? This is a somewhat difficult area because the number of patients is relatively small. As was stated earlier, the genotype 1 cirrhotics are perhaps the group that is most difficult to treat and using the same formulation with

the 48 week versus 24 and the 1000/1200 versus 800, it would appear that in general, the trends appear to favor the high dose of ribavirin in the 48 week, but it is a little bit difficult to make these conclusions because the numbers are small and it's even more of an issue in the non-1 population.

Genotype 4 needs to be mentioned here. And just to remind you, I am well aware of your expertise, but there are five different genotypes within the non-1 group. These genotypes are not -- there are more than five. These genotypes are not entirely uniform in their response to Pegasys Copegus. Genotype 4 is known from the literature to have intermediate sensitivity to alfa interferons and the data collected in the study was consistent with that.

There were 36 individuals, however, so we have to be very cautious in making too great an interpretation. It would seem that in looking at genotype 4 that 48 weeks appears to be superior to 24 and the higher dose ribavirin, the 1000/1200 milligrams appears to be superior to the 800 milligrams. However, when you're dealing with an n of

13 individuals, you probably are on shaky ground for making any large conclusions.

What about histology? Patients with paired biopsies. Two-hundred sixty patients underwent paired biopsy in this study and again, this is the same HAI score with less than two -- with a 2 point or greater decrease in the HAI score being interpreted as being a responder. In this case, it looks like in the portion of patients who had paired biopsies as though the number of responders is somewhat the same across all four study arms. There is some difference, but it's not very large and again, looking for the participation of what does the histology mean, this was -- whoops, we're getting ahead of ourselves.

The histology again was mostly inflammatory. The number of individuals that had a decrease in their fibrotic score was 19 of the 260 individuals and only 17 of those individuals actually sustained definition of being a responder.

DR. FLEMING: Could I ask one point of information before you leave. Dr. Tauber, you've been very careful and appropriate to recognize the

confounding in this randomization design when you were looking at sustained viral load.

Now you're getting into histology and the same confounding exists, but you're not accounting for it on this slide.

DR. TAUBER: Point well taken.

DR. GULICK: Can I ask that we hold further comments and then we'll come back in the question and answer period? Thanks.

DR. TAUBER: Moving on to adverse events. There were fewer severe and serious adverse events in the 24 week arms than in the 48 week. Dose reductions for Pegasys occurred in all four arms, but appeared to be highest in the 48 week 1000/1200 milligram ribavirin dose.

Dose reductions for ribavirin appeared to be lower in the 24 week 800 milligram ribavirin arm as was echoing what was stated by the sponsor.

What about serious adverse events? Serious adverse events incidence was higher in the 48 week arms than in the 24 week. The serious adverse events incidence was lower in the 24 week, 800

milligram ribavirin arm than in the 48 week, 1000/1200 milligram arm.

Serious infections had higher incidence in the 48 week, 1000/1200 milligram arm as you can see.

Next. To speak a little bit more about the serious infections, as you can see there was apparent increase as I just stated in the Pegasys Copegus higher 1000/1200 milligram arm for 48 weeks. These were again mostly bacterial. The recovered organisms were bacteria that you would common associated with normal human flora.

Again, the issue of neutropenia and lymphopenia is raised and I wanted to go forward at this point and talk and present two brief case reports from the two studies.

The first of these is a 68-year-old man who developed difficulty swallowing and fever on study day 33. On study day 47, severe neutropenia with an absolute neutrophil of 400 was detected and he was appropriately discontinued from his dosage of Pegasys and 1200 milligrams per day of Copegus. On day 59, hospital admission occurred with severe throat pain,

anemia, neutropenia and thrombocytopenia and this case was brought up earlier. Staph aureus epiglottitis was diagnosed by laryngoscopy and he was also noted to have staph aureus recovered from his urine. He was placed on high dose antibiotics, given red cell transfusions and made a very miraculous recovery.

On the -- what is not on here is that on day 65 his ANC had risen to a value of 1000. So he had had a response, but he still fulfilled the criteria of being neutropenic.

The second study is the septicemic death from the second study. This is a 45-year-old man who sustained a splinter injury to his hand on day 55. His treatment regimen was Pegasys Copegus 800 milligrams per day in divided dosage. On day 58 the splinter was removed. His wound was cleansed and he was noted to have an ANC of 800. On day 60 he returned for a wound check and at that time he was offered and refused antibiotics. On day 62 through 63, he developed a fever to 39 degree Celsius, agitation oliguria. By day 64 he was in frank septic shock, was admitted to the hospital in transfer from

his clinic. His admission ANC was 2600, but it was then recorded as being 0 within 12 hours of admission. His blood cultures great grand positive cocci, consistent with staph aureus and on day 65 he expired.

Neutropenia during treatment and follow-up, again looking at neutropenia, there was a lot of neutropenia in this study as well. There was the peak because was found mostly in the grade 3 area and about 5 percent as was seen in the first study, developed grade 4 neutropenia during the conduct of the trial.

Lymphopenia was also demonstrated in this study as it was in the first with a peak in the grade 2 area.

What about numbers of patients withdrawn? The incidence of withdrawal was lower in the 24 week arms than in the 48 week. Adverse events would more commonly cause withdrawal than laboratory abnormalities. Neuropsychiatric adverse events were the most frequent cause of patient withdrawal overall.

What about dose modifications? And I've done the same thing here just for reference. This peg-interferon goes with that 800 and this

peg-interferon goes with the 1000/1200 milligrams, but placing them side by side allows you to compare the performance.

Pegasys was most often modified for laboratory abnormalities which were predominantly neutropenia, thrombocytopenia and were pretty well the same in both of these two 24 week study arms.

Copegus in the 24 week arms were more often dose modified for adverse events than they were for laboratory abnormalities and the laboratory abnormalities, when they did occur were -- would be anticipated in the area of anemia.

What about the 48-week arms? Similar trends are seen in the 48 and the 24 week groups regarding dose modifications. Pegasys was modified more commonly for laboratory abnormalities than for adverse events. The most common laboratory abnormalities were neutropenia and thrombocytopenia. The neutropenia and the thrombocytopenia were higher in the 1000 to 1200 milligram ribavirin arms than in the 800 milligram arms.

Ribavirin was -- Copegus was modified more

often for adverse events than for laboratory abnormalities. Laboratory abnormalities were predominantly anemia and may have had a contribution to make in terms of the -- I'm sorry, were lower in incidence in the 800 milligram ribavirin arm than in the 1000/1200 milligram arm.

Lab abnormalities by weight. The same principles as we used in the analysis. This is descriptive. Looking at those individuals under 65 kilograms versus those that are over 65 kilograms. Consistently, the under 65 kilogram, there are four arms to the study, but in each of the four, the companion arm is lower in terms of hemoglobins less than 10. When you look at neutropenia grade 3 or higher, that same trend is found with the lower than 65 kilogram arm being somewhat higher in incidence than the companion arm of those greater than 65 kilograms.

What about BMI? Again, looking at the potential influence of obesity with being under 25, being considered to be fit and those over 25 or equal to possibly being obese. The hemoglobins again

reflect a very similar trend as found in the 65 kilogram cut point. As you see, the first arm, the under 25 in each of these couplets is taller, even though it's very, very much less discernible in these, the lower ribavirin doses than it is in the higher ribavirin doses. Neutropenia, again appears to be somewhat higher in the 25, in the under 25 BMI versus the over 25.

Conclusions. Sustained virological response in patients infected with genotype 1 had the highest sustained virological response when 180 micrograms of Pegasys and 1000 to 1200 milligrams of ribavirin were administered for 48 weeks.

How about the patients with genotype non-1? The sustained virological response was similar in all four treatment regimens.

What about genotype 4? Well, it seems highest with the combination of 1000/1200 milligrams of ribavirin for 48 weeks, but there really are too few patients to make a conclusion.

Response rates in the U.S. sites were lower compared to the non-U.S. and perhaps further

assessment is needed.

What about safety? Twenty-four weeks with Pegasys and the lower or 800 milligram dose of ribavirin compared to the 800 or the 1000/1200 milligram ribavirin compared to the 48 week therapy demonstrated lower incidence of severe or serious adverse events, fewer withdrawals and fewer dose modification of either the Pegasys or the Copegus. The 48 week 1000/1200 milligram ribavirin was associated with higher serious infections, withdrawals for neutropenia. The 800 milligram ribavirin compared to the 1000/1200 milligram ribavirin dose demonstrated lower incidence of ribavirin dose modification and serious adverse events. And there's insufficient data to assess neutropenia in serious infections and it was noted that it was a fatal infection study in which severe neutropenia was recorded.

What about the risk benefit that was derived from these studies? Well, therapy with 800 milligrams of ribavirin for 24 weeks compared to 800 or 1000/1200 milligrams of ribavirin for 48 weeks demonstrated less serious toxicity and similar

sustained viral response.

Are there unresolved questions? Well, yes. There are many factors that obviously affect treatment response and toxicity. The dose, the Pegasys and ribavirin and the duration of treatment, the HCV genotype and titers perhaps need further exploration, geographic and other baseline characteristics including weight might be explored.

Needs for additional studies, optimization of peginterferon and ribavirin dose and exposure. Weight base versus fixed dosing. Confirm the hypotheses raised by study 2 in patients with HCV genotype 1 and low viral titer and HCV genotype 4.

Is that it?

I believe that concludes my remarks. Thank you very much for your attention.

DR. GULICK: Thank you. At this point, we're going to open it up to the Committee for questions. I'd like people to really stick to points of information and questions of clarification, try to refrain from jumping into the issues that we will discuss this afternoon.

And these can be either of the sponsor or the Agency.

Dr. So, do you want to start us off?

DR. SO: Could you -- since we are being asked to approve this drug for the treatment of chronic hep C and patients with elevated ALT, could the -- could we define elevated ALT? Is it for inclusion in the trial, was that beyond a certain how many times above normal?

DR. HOFFMAN: Hoffman from the sponsor. Patients who had any elevation in ALT were permitted into the trial on two occasions prior to -- during the screening period.

DR. SO: So if the optimal limit of normal is 40, so if the patient is 42, he's eligible for enrollment?

DR. HOFFMAN: If he had two values which were above the upper limit of normal, the patient would be eligible.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: Ask a question about what you mean by high viral load. I think you misspoke the

level of virus as an average in the groups. It was 6 and 5.8. That wasn't 6 million that was 2^6, wasn't it? And $10^{5.8}$ in the various groups.

So how did you -- what was the set point for high versus low and how does that compare to the studies that were done with the other peginterferon alpha-2a? Because I believe you used a different methodology for measuring high versus low viral load.

DR. HOFFMAN: No, actually when we designed these studies it was still fairly early on. It was back in 1998 and 1999, so it's still two million. We since that time moved on to the international units where we defined as 800,000, greater than 800,000 or less than 800,000.

DR. HOOFNAGLE: But is that two million similar to the two million obtained in the previous trials reported by Schering? I believe they used the NGI assay?

DR. HOFFMAN: That's difficult to say because of the difference in the techniques.

DR. HOOFNAGLE: And did you look at any other cut points for high versus low? This is

important for your second trial where you had the stratification and so forth which showed that it looked like even with a low viral load, genotype 1 patients had a higher response with longer therapy?

DR. HOFFMAN: No, we did not. We looked at 2 million. However, your point is well taken.

DR. HOOFNAGLE: Then I'd like to point out that this is a little bit higher viral load than reported with the previous product. It's more likely a bit higher.

DR. HOFFMAN: Two million versus two million?

DR. HOOFNAGLE: Yes.

DR. GULICK: Dr. Kumar?

DR. KUMAR: Dr. Hoffman, could I ask you what is the difference between your ribavirin product and the Rebetol that's currently available other than one being capsule and one being tablet. Is there any inherent differences between the two products?

DR. HOFFMAN: No. The ribavirin is the same chemical.

DR. KUMAR: And can I follow up with a

question? As a clinician, will I be able to rite for your product separately or will it be bundled and will I be able to use it only with pegylated interferon?

DR. HOFFMAN: No, application contains both products as separate components.

DR. KUMAR: Thank you. Could I ask you how you determined depression in your patients? At each site did they actively ask the patients about depression or did patients complain about depression and then was it recorded in the case support form?

DR. HOFFMAN: Yes, this is an area of some methodological problems because there's really no good depression scale that's appropriate for interferon therapy. We don't believe the Becks is the right scale for it as well. And if you ask patients directly about any adverse event you tend to get a higher incidence than if you just wait for them to volunteer it.

So in our studies, what we did is we measured depression according to what patients volunteered.

DR. KUMAR: Thank you.

DR. GULICK: Dr. Sun and then Dr. Wood.

DR. SUN: In the Phase 3 studies for patients that weighed more than 75 kilograms, they could receive either 1000 or 1200 milligrams of ribavirin. How was it determined which dose they received?

DR. HOFFMAN: Here's the clarification. If they weighed less than 75 kilograms, they were assigned to 1000 in that group. If they weighed 75 kilograms or more, they received 1200.

DR. GULICK: Dr. Wood and then Dr. Fletcher.

DR. WOOD: I have several questions regarding African American patients in your studies. I'm very concerned in terms of the response rates because in the first study there was really no difference among the African American subpopulation.

My first question is in reviewing the pharmacokinetic data, you report in your report breakouts according to weight.

Do you have any data specifically that looks at pharmacokinetics in African Americans?

DR. HOFFMAN: Yes, we do and Karin Jorga of clinical pharmacology will respond.

DR. JORGA: We did a population of pharmacokinetic analysis in our Phase 3 pivotal trials and we looked at the effect of covariates and pharmacokinetics of ribavirin and could I have the slide up, please? This is what you are seeing here. This is the influence of race on the clearance of ribavirin. There is a difference. The African Americans have a higher clearance which leads to low exposure in this population. The difference, however, is relatively small if you look at the scale. It's around 20 percent difference between these two races.

DR. WOOD: My next question and follow-up to that is regarding African Americans, do you believe that the lack of responses due to a greater prevalence of genotype 1 in the African American population? I'm trying to get historically why African Americans don't seem to respond as well as Asians or Caucasians to interferon alpha and ribavirin therapy. Did you look at that from the genotype 1 standpoint?

The other question is that since

non-genotype 1 patients appear to respond much better than genotype 1, did you see that kind of same response in African Americans who are non-genotype 1?

DR. HOFFMAN: As you mentioned, the numbers of black Americans who participated in the study is quite small and the vast majority had genotype 1, so we really weren't able to sort that out and because of the low numbers that were in our trials we have two studies going on. One is a U.S. study that's being sponsored by Roche looking at 100 patients. We're looking at African Americans versus Caucasian patients. They're receiving Pegasys 180 micrograms plus the full dose of the Copegus. They're all genotype 1 patients and we're following them to see what happens.

In addition, there is the viral hep C study which is an NIH collaboration of 400 patients, half African American, half European American that's looking at the same question. The U.S. study should be completed next year. The NIH sponsored trial in 2004-2005, so we fully agree with you. We don't have the information to sort out what the reason if for

what we see as a lower response, but hopefully these two trials between them, we'll get some answers.

DR. WOOD: Thank you.

DR. GULICK: Dr. Fletcher and then Dr. Wong.

DR. FLETCHER: This question is probably both for the FDA and the sponsor. I'm interested in this issue of body weight and its association with response. And the first one is is it possible in the analyses of response of sustained viral response to adjust for body weight and then look at this whether there is a geographic difference?

DR. SIEGEL: The geographic differences are interesting in a number of regards. In all of these studies, the U.S. population which -- in both of the studies which had a lower response rate, on any of a number of factors known to contribute to response rate had a less desirable outcome which is to say, had a less desirable baseline characteristic which is to say were more likely to have genotype 1, were more likely to have higher viral load, were more likely to be overweight and what else am I leaving out,

cirrhotic, more likely to be cirrhotic.

When you do a multivariate analysis, the impact of region looks like it plays a relatively small factor. Those factors don't fully account, taken together, for the differences observed. There may be treatment practice differences in terms of pushing dosing through toxicity and so forth as well. I don't think we have ever had reason to believe that there's something about whether you live in Europe or U.S. that influences response rates. Most of the differences -- but it is worth noting that this is a study that is done predominantly outside of the U.S. and one of the reasons we highlighted that is that this field, both in academic settings and somewhat in commercial settings has -- had a lot of cross study comparisons saying well the response rate was X here, and Y here and it's important to know that a lot of factors such as region, for example, where you do the study could account for several percent differences maybe even in the 15 to 20 percent differences in response rate because of this multiple factor situation and those cross study comparisons which

because there's no randomization would in any case be highly suspect and I think in these cases are clearly problematic.

DR. FLETCHER: Just to go along with that, do you see the opposite trend if you look at toxicity, because you would think if weight is really associated with response in toxicity, you would think you might see higher rates of toxicity outside of the U.S. because you have a smaller body weight population. I'm just wondering do you, at least numerically, do you see that trend as well?

DR. SIEGEL: No, not clearly, but I have to say across a broad range of studies and a broad range of diseases we tend to see lower toxicity rates outside of the U.S. than in the U.S.. I think it's probably -- and it's certainly been true of interferon in cancer trials. There was a trial, Italian trials and Texas trials. I remember in CML, but in many other cases as well as in multinational trials, I suspect that it's generally an issue of ascertainment. Either the patients, how much they're willing to present it, how much the physicians are to elicit it.

So those comparisons, unfortunately, are really difficult to make in a meaningful way.

DR. GULICK: Dr. Wong and then Dr. Alter.

DR. WONG: I have a question both for the sponsor and the Agency. I was concerned as I reviewed the data and also heard the presentations today that there's such a heavy focus on the endpoint of sustained virologic response and that alternate measures of response that might well correspond with long-term clinical benefit were not analyzed nearly in as great detail nor given as much weight.

I guess my question is first of all am I correct in interpreting how you folks all analyzed these data and interpreted these data, and secondly what do we know about the relative predictive value of various indicators such as sustained virologic response, sustained biochemical response, the combination of those two as was outlined in the protocol for the first study, but was not really analyzed in detail for us today and I'm particularly interested what do we know about the predictive value of histologic response as compared to sustained

virologic response in predicting that a patient will or will not do well in the long run.

DR. HOFFMAN: A couple ways to answer that. First, regarding your question of what is the meaning of sustained virologic response. We have now, actually data outside of Pegasys and data that we're generating now suggests that sustained virologic response is actually a very good measure of long term virologic response. In our program, both for monotherapy and in combination therapy, we had about 500 patients now who are sustained virologic responders followed for up to four years. Of those patients, 99 percent are still undetectable. We're following them yearly, bringing them back. There's a questionnaire they fill out regarding their ALT, regarding their HCV RNA, regarding if they've had a biopsy, if they've had any liver-related morbidity or mortality.

So much work has been done including some early work done by Dr. Hoofnagle. It appears that sustained virologic response is a pretty good endpoint.

Is that a good surrogate for long-term outcome? I'm going to ask Dr. Schiffman to come up and just give a brief description of the HALTC trial that's being conducted within NIH.

DR. SHIFFMAN: I think there are two lines of evidence that can answer your question about long term outcomes. Number one is in the sustained patients with sustained virologic response there are a couple of published studies that have looked at follow up liver biopsies two to fives years after achieving sustained virologic response which continue to show histologic benefit, compared to the baseline at the end of treatment, implying that once this long term eradication of virus, there is a continued improvement in liver histology over a prolonged period of time.

The second issue which is much more important is the nonresponders, if you get a transient improvement, I think that's where your question was going to. And there's two pieces of evidence there. One we have and one is on-going. The first is a study we conducted at our unit where we took patients who were nonresponders to interferon therapy and

randomized them to continue maintenance therapy and to stop therapy. In the group that stopped therapy, we saw a regression or return of the inflammation back towards the baseline within a year of discontinuing therapy and over a two-year follow-up period a slight, but not significant increase in fibrosis.

There's currently a large multi-center sponsor NIH sponsored trial which have been referred to already as the HALTC trial. We are also one of the centers in that trial. And this trial will randomize nonresponders to Pegasys and Copegus to continue Pegasys monotherapy long term over approximately three and a half years versus a control group that is not receiving further therapy, to try to answer that question, will the control group receive a long term benefit from that initial treatment or can continuous maintenance therapy and viral suppression give better long term benefit in terms of hard clinical outcomes, decompensation, progression to cirrhosis, development of liver cancer and need for liver transplantation.

DR. WONG: So if I can just follow up. I guess the answer to -- the congruence of the first

question is if you have a response that's measurable, but it's not complete or sustained, is that a response that's worth having? And I guess the answer to that is we don't yet know. Is that fair?

DR. SHIFFMAN: By response to the treatment you mean a normalization --

DR. WONG: Reduction in the viral titer, but not too undetectable and normalization of the biochemical parameters and perhaps even substantial improvement in histology, but does not achieve a sustained viral response. Is that response equivalent to no response or do we just not know?

DR. SHIFFMAN: I think --

DR. WONG: In a sense I mean I interpret some of the interpretations of the results of these two trials today as equating a response like that to no response at all.

DR. SHIFFMAN: I think there is -- in the study we conducted where we saw exactly what you're saying, a drop in viral load and an improvement in histology during therapy, when we stop therapy, that improvement was short lived. Virus returned back

towards the baseline and within one to two years on follow up liver biopsies, the inflammatory component was back -- not significantly different from baseline as well.

There's a recently published large follow-up study of patients who received interferon therapy in Japan and what that shows is sustained virologic responders have a significant reduction in long term mortality whereas the nonresponders, that benefit was questionable.

DR. GULICK: Would the Agency like to respond to this, too?

Dr. Siegel?

DR. SIEGEL: Yes, let me talk a little bit where we've been, at least from biologics perspective, although we work closely with Center for Drugs and my comment on differences, if there are any, of significance.

We, over the years, we've had a gradually shifting approach as has the community to the relative significance of liver enzymes biopsy and as it's become available and then more reproducible and better

validated viral load.

In recent years, in answer to part of your question and even over the time course of these studies, we've moved away from combined viral and biochemical response to viral response along as our area of primary interest. And the reason for that has been because of a look at discordant responders. Those patients who have persistent absence of detectable virus, but some elevation of liver enzymes often have, appeared to have transient elevation of liver enzymes. It may well be for reasons unrelated to the hepatitis itself and we've not seen evidence, although we don't have huge numbers that those patients are still infected or for that matter still have progressive liver disease.

Conversely, those patients who still have viral infection, but normalized liver, I think there are important questions that were just discussed to be answered as to whether there are benefits to suppressing the amount of virus, but absent a sign that the infection is cleared, we have not decided that this endpoint is sufficiently indicative of

clinical benefit. In a sense, these are all surrogate endpoints, but conducting these trials to achieve any significant incident of clinically meaningful outcomes, cancers and bleeding, ascites and decompensation of various sorts would require extremely large numbers and in many cases many years or decades to achieve those events and really be a significant problem.

In general, in infectious diseases when we have a good validated measure of the infectious cause, and it seems to be eliminated in a persistent way although in the earliest trials end of treatment factors were measured, we assume they're in that six months off treatment was far more predicted of long term responses, as you've seen.

So that's where we are in balancing all of that. We're looking for dominant -- oh, I should say that liver biopsy is something that we've always felt is potentially closer from a theoretical basis, it's certainly been liver enzymes, anyhow closer to a predictor of benefit. It has some significant limitations. One is that it's very hard to get a high

level of follow up on liver biopsies. Even among the subpopulations where one chooses to try to seek them, success, I don't know for sure in this study, but typically ranges from as low as 30 percent up to as high as 80 percent, but rarely higher. So there's significant amount of missing data. It will tend to be significantly biased. If a treatment is less effective on viral load, the patient is more likely to drop out and less likely to show up for their liver biopsy.

And most, but not all, most of the effects, the more predominant effects that are observed on liver biopsy at least over the first year or two, when you look at the raw scores are inflammatory cellular infiltrates. We do see effects as was noted on the extent of fibrosis, but less so, so it's likely not to be a highly sensitive indicator of treatment effect differences, if you believe that the differences that you see in SVR are real differences. It's certainly a less sensitive indicator and hard to interpret because of the missing data.

DR. GULICK: Okay, I have Dr. Alter, Sjogren and Johnson and I'm going to allow --

DR. FLEMING: Before we leave this, could we'd query, Jay?

DR. GULICK: Sure.

DR. FLEMING: Jay, I'd like to follow up because this -- your insights here on this are really critical and I think Dr. Wong's questions are raising a very key issue as well.

Is there any evidence that you're aware of that truly is an intention to treat type of validation that would say that effects on sustained virologic suppression for a period of 24 weeks or for a period of whatever, in fact is predictive of cobenefit. Now I realize what I really want to know is progression of cirrhosis, need for a liver transplant, hepatocellular carcinoma, but even at an intermediate level, meaningful changes in histologic progression, is there any intention to treat type of validation that truly is a surrogacy validation, not a correlate, but a surrogate? Is there any evidence of that nature at all here?

DR. SIEGEL: I defer that to the hepatologists. None that I'm aware of. There's evidence, you heard some of it of varying sorts that suggest a relationship there, but in terms of an intention to treat from a randomized study, no. Not that I know of.

DR. SIEGEL: But we know throughout clinical research that correlations are frequent and true surrogacy is rare.

DR. GULICK: Can we have some backup, perhaps, by some of our hepatologist consultants? Dr. Hoofnagle?

DR. HOOFNAGLE: We simply don't have a group that has been followed and not treated, but one can say in the patients who do have a sustained virological response that over 95 percent remain in long term follow up as long as they've been followed, PCR negative, the majority have normal enzymes and many in long term follow have had a normal liver biopsy, actually, sort of a resolution.

So it looks to be very solid long term endpoint. This virus replicates very quickly so that

once you stop therapy it comes roaring back usually in the relapse pretty quickly. It's a strange person that waits three or four months to relapse. After six months, again it's less than five percent, probably less than two percent that will relapse after that.

DR. SIEGEL: Just a comment on the surrogacy being rare. There are some people who would call the measurement of viral load in this disease not a surrogate endpoint. It's clearly not a clinical endpoint. It depends on how you look at it, but let me say that the sustained absence of the pathogenic organism in an infectious disease is in many cases a good predictor. So if somebody -- if you give somebody a course of say antibiotics for a urinary tract infection and they're culture negative for a long period of time, changes are that the clinical sequelae and the clinical symptoms are going to be gone. So we're dealing with a -- if you choose to call it a surrogate, one that's pretty close to the pathophysiology of the disease.

DR. FLEMING: Obviously, as you're pointing out, Jay, there's a whole continuum in what

the reliability of a predictor or correlate may be and I think that's what Jay is saying as well. If we're talking about the reason -- the reason that we're relying on these markers and they are markers is that these clinical phenomenon might be 20 to 40 to 50 years down the road. I worry a lot about whether what we're seeing in six months is going to predict an effect of magnitude to effect a clinical event 20 to 40 years down the road.

Now if what we see at six months, in fact, is reliably predicting the effect on viral levels 10 years later, then certainly that is much more compelling.

DR. GULICK: Dr. Wong, a follow up question?

DR. WONG: I guess I asked that question not really because I would dispute the idea that achieving a sustained viral response is desirable. That's obviously desirable. But I guess the deeper question is some response that's less than that is also desirable because what we're asked here is to look at some analyses of subgroups, for example, in

which there are relatively small, but not zero differences in response rates between those subgroups. But in those subgroups also, for example, the histologic responses are higher than the sustained virologic responses. Are those levels of response -- are those other responses to be ignored or are they real and possibly beneficial?

DR. HOFFMAN: If I could comment on that? Hoffman.

When we discussed our endpoints with FDA and we worked together on developing these protocols in monotherapy it was agreed we should try to get biopsies, liver biopsies on as many patients as possible.

In the combination therapy program, as we discussed it, and as Dr. Siegel mentioned, there's been a movement away from the liver biopsy. There's also as responses have gotten higher virologically, patients have become less willing to have them. So in fact, in our original protocols, we did not even have histology as an endpoint in these protocols. However, in discussing our protocols with other authorities and

with investigators, consultants, they felt we should get some information.

Because patients who don't respond by 24 weeks virologically shown in virtually every trial, whether it's monotherapy or combination therapy, don't go on to then subsequently have a sustained virological response. Patients leave the trial and were permitted to leave the trial. So the ones who had the biopsy tended to be the ones who were the responders. And that's why the numbers are, I think, are so very high.

DR. GULICK: Dr. Hoofnagle, can you help us a little bit more?

DR. HOOFNAGLE: What Jay mentioned is the real problem, is that you can't get a good sample of liver biopsies from all the patients, so it's a lot of bias put into the system by that.

Also, you know the liver biopsy can change just like the ALT can change. And with a year of interferon therapy, you get a benefit, you can do a biopsy on treatment, even on nonresponders. That benefit slowly goes away. So it depends on when you

do the biopsy whether you see a benefit. And then you have people treated for 24 weeks. Others treated for a year. There's going to be variability.

Because it's so difficult to do a biopsy, even though I'm a hepatologist, I believe it's not very useful as an endpoint any more in these types of trials.

Let me also, I'd like to make two other comments. One is about the comparison geographically. There's another very big variable and I think it's been downplayed a little too much and that is age. The Americans were older, response goes down with age. And what goes up with age, obesity and weight as you all know. So in talking about weight, you really have to control for age whenever you do that.

I know the Americans are overweight, but even comparing them for weight, there's a lower response rate in the Americans. It's quite striking. And I know it's not because they live in America, but it is probably due to the strain of genotype 1 that we have in America, may be relatively more resistant.

DR. GULICK: Okay. I want to go back to

several Committee Members who haven't had a chance to ask questions and then we'll come back to others if there are some follow up questions. So I have Drs. Alter, Sjogren and Johnson, waiting patients. Dr. Alter?

DR. ALTER: Thank you. I actually would like to go back to some questions on the analysis that either the data weren't stratified in that way so that we could see it, whereas the analysis might have been done.

First, to follow up to Dr. Woods' question on African Americans. I understand -- or on blacks -- within the study. I understand that the numbers were very small and therefore you can't draw any conclusions, but my curiosity overwhelms me and if I understand it correctly, based on some stratified data provided in the FDA summary, the African Americans most of whom, virtually all of whom had genotype 1, have a stay in virologic response of 22 percent and so that would be about half of what all genotype 1s had. Is that correct?

DR. HOFFMAN: Yes, we have a slide here.

DR. ALTER: Just refer to combination therapy for a moment to make it easier.

DR. HOOFNAGLE: Dr. Duff?

DR. DUFF: As has been pointed out by the Committee, we've been somewhat reluctant to draw broad conclusions from the patient numbers certainly. And what we've got here is the racial breakdown in terms of Caucasians versus blacks. To really break things down beyond this, we have not done, simply because we feel that the limits of the data that are really measured in the teens, would be less helpful and I don't have those numbers right now. But what we can say broadly as has been reported by others, that there is certainly a reduction and an apparent reduced virologic response rate for these patients, many of whom are genotype 1.

It's for that reason that we feel the best way to really get a handle on this is going to be prospectively in the studies that Dr. Hoffman has outlined.

DR. ALTER: I understand that. I just wanted to confirm that among genotype 1 patients. You

were seeing the same difference about twice, and that's all.

DR. DUFF: Thank you.

DR. ALTER: I'll move on. With respect to some of the other differences that have been brought up as possibly important, I'm concerned about the types of analyses that have been done and whether or not these differences are real, are factual, based on small numbers because of the many stratified groups, based on a variety of others and so I'd like to ask -- we really do have two groups here. We have genotype 1 patients treated. We know that appears the optimal therapy is 48 weeks with the higher dose and then you have genotypes 2 and 3 who can be treated for 24 weeks with a lower dose and I'm just talking about combination therapy.

And based on, for example, U.S., non-U.S., among genotype 1 patients, you still see apparently a difference. But what about all of the other characteristics that might be different between the U.S. patients who are genotype 1 treated for 48 weeks at the higher dose and non-U.S. patients who have

genotype 1 treated for 48 weeks with the higher dose of combination therapy, taking into account age, gender, body weight, race. Then do you still see -- I couldn't tell how much of a difference there really was. It didn't actually look that great to be quite honest.

DR. DUFF: I am not sure, you'll have to help me to see if I'm responding exactly to your question, but I think we can begin to explore the area that you've raised. What we have seen, certainly in observing this finding about U.S./non-U.S. is that as has been pointed out by the medical reviewer, there are more frequent, poorer prognostic factors occurring in the U.S. and if I could slide up, please, we'll just quickly review the percentages, taken as single variables, first of all.

You will note, as has been pointed out, greater proportion of genotype 1 patients, patients who are older, patients who are heavier, patients who are more frequently cirrhotic, patients who are more frequently black or African American, patients who are less frequently Oriental which would be seen as it

certainly has been associated with more positive -- higher SVRs, viral load, but less dramatic. And we did perform a multiple logistic regression analysis which I'd be happy to put up, please. This will be -- should be next slide.

I believe -- yes, slide up, please. Perhaps you beat me to it. What we see here in terms of -- factoring all of these things into a model is that the overwhelming and predominant impact which essentially overshadows everything else in the model is genotype which I think is to your point. We see in descending order a number of other factors which certainly are playing a role and are confounding any attempt to analyze on a single factor and this has certainly been the challenge in interpreting the data.

We do note, for instance, here pretreatment viral load has an impact. Age has an impact. Baseline ALT quotient, whether a patient is or is not cirrhotic. We do note as has been noted by others the impact of weight as a confounder, I'm sorry, as predictor of response. But really, coming down towards the bottom of the list and in our opinion

some are washed out by the other factors is the regional difference and that's really the bottom line.

DR. ALTER: So are all of these significant or are some of these significant and some not, statistically?

DR. DUFF: What I'll do then as a backup, I'll pull up slide 43. We've gone on because genotype is so overwhelming and we then looked at the breakdown, taking genotype out of the equation, if you will. Okay, and you'll see here for the genotype 1 population which comprises about two thirds of our data set, that the significant factors are towards the top and the odds ratio as listed and region, you will note, essentially, falls in with a very modest odds increased odds ratio of 1.27 which is not statistically significant.

If I could have the next slide, we're getting into somewhat smaller numbers here, but if we look now at our non-1s, the factors that fall out here are as follows. We see that race, we see that the transition from body weight less than 65 to 65 to 85 kilos has an increased odds ratio with a P-value of

0.1. We're really not seeing much in terms of the transition from 65 to 85 to greater than 85 kilos, however. And histologic status. And again, region playing out further down the list, in general, and so our overall interpretation looking at the data in toto is that genotype is the driver and that when one is trying to interpret any given factor, one must be very careful about confounders and trying to really factor everything into the model before we draw conclusions.

DR. FLEMING: Before you leave this, just to hep clarify your question, you're looking in that analysis at region as a predictor and my take from this is that a good amount of the U.S./non-U.S. difference as a predictor can be explained by the confounding with these other factors.

A separate question though is region, in effect, a modifier in this multivariate analysis that adjusts for all these other factors, is the evidence of treatment effect within U.S. and non-U.S. apparent or is there an apparent difference or how strong is the evidence of effect in the U.S. in this model that takes into account for these other predictors?

DR. HOFFMAN: I think with all the confounders that there are, I think it's hard to know. As Dr. Hoofnagle said, is it possible that there are differences, not in the host so much as there are in the virus, particularly genotype 1 from Europe and the U.S. or from Asia and maybe is that the factor, but we don't have enough information to say.

DR. FLEMING: So there's not a specific answer then?

DR. HOFFMAN: Correct.

DR. ALTER: No, but I do think that based on this I think that the regional differences are really not a factor in terms of response when you contrast with a variety -- with everything else, particularly the most important ones. And I guess, I think that it's a problem when we know that we have a factor that is so overwhelming like genotype to present data actually without considering such an overwhelming factor and it's almost uninterpretable. And so I think that it's important plus while you can do multivariate analysis on the whole group, if you have an overwhelming factor, the black box always

doesn't take care of it and I think stratifying by genotype and then doing a multivariate analysis was exactly what I was looking for and I think it really does put some of these other factors into perspective.

DR. GULICK: Let me just caution people again. There's always a tendency to want to jump into further discussion of the issues which is what the afternoon is for.

DR. ALTER: I'm sorry.

DR. GULICK: No, that's okay. It's a good point to make at this point, but for others, let's try to finish off just with a couple more questions. I have Dr. Sjogren, Johnson and Englund in line and then I'm going to come back to people who have already asked some questions.

Dr. Sjogren?

DR. SJOGREN: I wanted to make sure I understood how the data was analyzed to begin with. The study 15801, we were told that all patients that were randomized were indeed put into the analysis and so there's an intention to treat.

The second study, 15942, Roche and also

FDA told us that the patients that were presented to us were intention to treat, but then there was a caveat that they were patients that took at least one dose. And so that is not intention to treat in a strict way, but rather patients that were randomized and took medication. So I want to make sure that we understand perfectly how the analysis was done.

DR. DUFF: Certainly, as a point of clarification, you're correct. The first study was initially presented as an all randomized, this was protocol to find. And then I presented some follow up, all treated data, in that patient subset. All treated being defined as randomized and having received one dose.

Based on protocol amendments that occurred prior to data base close, the analysis for the second study, the dose and duration study, was the primary was derived on an all treated and just to clarify the definition, patients had to be randomized and receive one dose.

In terms of how they were handled from then on, if there was a loss to follow up, if there

was a premature withdrawal, etcetera, these would have been considered nonresponders.

DR. SJOGREN: Thank you.

DR. SIEGEL: Let me just add to that from our perspective that I think you're correct, that's technically not an intent to treat. It is, however, an analysis that we accept without concern when it's pre-specified in the protocol. If the study is fully blinded so that the decision to drop out before the first dose could not be influenced by either knowledge of what you're randomized to or by a drug effect, because you haven't received any, then we presume that outcomes in those patients are probably noise and can be safely excluded and so it's called more appropriately modified intent to treat probably.

DR. SJOGREN: I understand. However, when you think of both studies, at least myself, got in a mental set and for the first study, it's a very rigorous way of looking at data and then I translate that to the second one. If you tell me it's intention to treat, but indeed it is not comparable to the first study and I think although acceptable, like you said,

you need to develop a different set of mental skills to evaluate that study in its own right.

I have a couple of other questions. Slide 49 of Roche. We were shown the genotype 1 by viral load and I'm interested in the high viral load. We have 39 percent for Pegasys and Copegus and 32 percent for Rebetron. And I wonder if there was a statistical significance between the two of them? All the other slides or most of them have statistical levels, but not this particular one and I'm interested to know.

DR. GULICK: Can we put that slide up?

DR. HOFFMAN: Frank Duff?

DR. DUFF: Thank you. The reason that there were no P-values added here is that this was a descriptive representation of high and low viral load, the P-values that you've seen previously in the larger data sets reflected the statistics there. So this is really a descriptive evaluation and the reason this was performed is that we were interested in determining whether trends might exist in terms of the three treatments that were similar for both low and high viral load populations and that's the reason that

I showed that today.

DR. SJOGREN: Well, we ask then to my statistical colleagues if it would be appropriate to run statistics in those numbers. They look fairly sizeable to me and fairly comparable, 182 and 189 and maybe this is something for the afternoon, but it's something that I have another thought, probably very incorrect because there are different studies, but I made a rough calculation. We were told that 37 percent of these patients were U.S. based. That translates to about 890 patients of the two cohorts of patients and that's a sizeable number. And I wonder if we need to look at a dose of 890 patients in terms of their response to genotype 1, since you know they received fairly similar treatment, Pegasys and Copegus, a large number of them. And I don't think we should lose that opportunity to indeed establish some more determinations.

In slide 66 of the presenter, we are told that we can indeed perhaps predict who is going to respond and who is not going to respond by looking at 2 log drop or negative RNA and I wonder if that dose -

- that data analysis was powered? If the study was powered to make that kind of decision? I know that this afternoon we're going to have to recommend to FDA whether to accept it or not and I think it is very important for us to know if there was enough power to make those calculations or it's just a gestalt.

DR. HOFFMAN: This is descriptive. We're trying to find, based on our monotherapy where we found a negative predictive value of 98 percent, we intended to do this. It's not in the original protocol, but once we saw the monotherapy we were interested to see if we could find it again. So it's not powered but we do think that the results are compelling.

DR. SJOGREN: And finally, I know we discussed a lot about liver biopsies and I wanted to point out because I may be incorrect and I know there are further studies that is looking at the possibility of improving the livelihood of our patients with Pegasys and with ribavirin, but in these studies although the biopsies with all the problems that we encountered doing biopsies, the first study had a 7

percent, calculate 7 percent improvement in fibrosis, so the majority of the effect we've been told on inflammation and the second study, I calculated by the numbers that were given by the FDA, a 15.6 percent improvement in fibrosis. And so when we look at long term in terms of cirrhosis and fibrosis, it's interferon now doing the job in terms of -- and I want to know if I'm correct in my percentages because you know I just used my hand calculator.

And so although I am a believer in that negative RNA and eliminating the virus is very much what I want to see in my patients, I'm using a different hat at this Advisory Committee and wanting to know if indeed these numbers, I mean they're very small in terms of improvement in the fibrosis and liver biopsies.

DR. HOFFMAN: If I could comment first about the way that we did the analysis. What we used was the Nodel and the problem with Nodel is that it has a 4, 3 and 1. It doesn't have a 2. The better way now is a newer evaluation system called the Medavir system and I think in HALTC they're using a

more expanded fibrosis scale, the Ischac score which will allow for differences to be found. So we admit up front that the test that we used was more appropriate for inflammation.

DR. GULICK: Dr. Johnson and then Dr. Englund?

DR. JOHNSON: I had a simple question, just clarifying protocol guidelines for grade 4 neutropenia. Dr. Solsky said nobody required GCSF. I just wanted to understand were there guidelines in these protocols for the clinician to decide that they were going to give GCSF or was that up to the physician's discretion? It's on slide P-78.

DR. HOFFMAN: There was no -- in the dose modification or toxicity section, safety -- toxicity section where it said when to use GCSF. However, to treat the patients, clinicians were allowed to do it. We've changed that now in HIV HCV protocol. We are allowing -- we do say they can use it freely. We didn't really address it in the protocol.

DR. JOHNSON: And do you know what level of absolutely neutrophil count people are instituting

GCSF beyond just stopping drug and then doing dose modification?

DR. HOFFMAN: Do you want to comment, Jonathan Solsky?

DR. SOLSKY: I just would like to comment in regards to the entire clinical trial. The data base of the 1735 patients that we had, there was only one patient actually who got GCSF in that entire group. And that patient had an ANC of 280. The patient had no symptoms of infection, was withdrawn from therapy, was hospitalized to get GCSF and did well.

DR. GULICK: Dr. Englund.

DR. ENGLUND: Yes. I have a question about dose modification and actually that's on Table P-72. We're seeing that a third of the patients got doses modified and a third is an incredibly high amount in my opinion for a clinical trial.

Do you have an analysis of who got doses modified? Was it African Americans? Was it the heavy people? Was it the old people? And do you have information on the outcome in those who did have the

doses modified? Were they having more drug effect and therefore it was effective or it wasn't as effective?

DR. HOFFMAN: Yes. It's a -- first of all, you have to remember that dose modification would be one held dose. It could be one reduced dose. So these aren't necessarily permanent. They could be temporary or they could a skip dose. And when you try to analyze it because of that heterogeneity, it makes a bit difficult to draw conclusions.

What we can say is that the withdrawal rate is only about 10 percent in the trials so that dose modification was effective, from a safety point of view.

From a efficacy point of view -- can you put the slide up? This is admittedly a gross analysis that tries to look at the amount of drug that patients got called an 80/80/80 analysis where patients in order to meet the criterion needed to receive 80 percent of their doses of the components for 80 percent of the assigned time. And what can say that if patients meet the 80/80 rule and this is from the second study, the 942 duration and dose study, 76

percent of the patients for sustained virological responders, this is actually in the group who got the full dose and the full duration.

Patients who didn't meet 80/80/80, but continued to get drug, it did drop a bit to 65 percent, but it was still a fairly high response. Patients who failed to meet and prematurely discontinued only had 22 percent. So I think albeit this isn't the best analysis to look at it, if patients were dose reduced, they tended to stay in the studies and they tended to still have a good response.

DR. GULICK: Follow up?

DR. SOLSKY: Could I just add a little more in terms of answer to that dose modification question? If one looks actually in the premature withdrawals and looks at those in terms of discontinued for specifically anemia, thrombocytopenia or neutropenia, it was actually 2 percent. We had seven cases in that first study. So it's a relatively small number --

DR. GULICK: Can you speak up a bit?

DR. SOLSKY: I'm sorry. Do I need to

repeat myself?

DR. GULICK: Sure.

DR. SOLSKY: In terms of the premature withdrawals that were noted for blood abnormalities, anemia, thrombocytopenia or neutropenia, it was 2 percent of the entire group or 7 cases in the Pegasys-Copegus arm in the 801 study.

DR. GULICK: Dr. Fletcher, a follow up?

DR. FLETCHER: Yes, I just wanted to follow up, slide P-88, if I'm interpreting that slide correctly, at least for anemia, the majority of those dose modifications were permanent, however.

DR. HOFFMAN: Yes. That's correct.

DR. ENGLUND: And they were for ribavirin. I'm also interested in not just the Pegasys, but the ribavirin component.

DR. SOLSKY: Yes, in terms of just the ribavirin component, down here, if you look, there were actually 9 of the 49 patients who had their ribavirin discontinued, but continued on Pegasys and continued on therapy.

And in terms of permanent discontinuation,

for ribavirin, as you can see, it was 8 percent.

DR. ENGLUND: That is permanent dose reduction?

DR. SOLSKY: Dose modification, yes.

DR. FLETCHER: It is 8 percent, but again, isn't it 34 of the 49 patients? Could you put that slide back up? It's 8 percent, but isn't it 34 or 49?

DR. HOFFMAN: I'm trying to remember. It's a while since we designed this study. I know that we -- I'm trying, do you know if we allowed them to go back up?

DR. SOLSKY: The way that the protocol worked was that they would reduce their dose to 600 and then the physicians could go up to 800, but they could not return them back to their original dose.

DR. HOFFMAN: If I could add to that, that wasn't the case for Pegasys. With interferon side effects often there's a tolerability that develop. You can go back up and that's why a lot of the dose modifications on Pegasys were not permanent, but were temporary.

DR. ENGLUND: And I have one other short

question for the sponsor and that is in view of the concerns of potential teratogenicity of ribavirin, real or not real, have they analyzed the affect of birth control and the various methods of birth control on the patients who are receiving the drug? Although we know that mainly males were tested, but still I'm concerned about the difference in oral birth controls versus Depo and if that has been looked at.

DR. HOFFMAN: I don't believe we did that analysis. A lot of the pregnancies were actually in the partners of the males which makes it difficult to get the information for confidentiality reasons. We don't have the answer.

DR. GULICK: I want to make sure that everybody on the Committee who hasn't asked a question yet is happy.

Dr. Fleming?

DR. FLEMING: Two questions, one on each trial. One of them follows up on Dr. Alter's earlier comments. It is extremely important to look at the imbalances that may exist here in genotype. We know that there was a stratification done by those who had

high titers in genotype 1 and this group is very different. If you look at the aggregate response rate, we see 35 percent have sustained virologic response in this group. The aggregate of all the rest have twice that high in terms of their response. Now the sponsor and the FDA were careful when we were looking at the analyses of sustained virologic response to then keep these categories separate, but for example, when we looked a histologic response, when we looked at overall safety, we then ignored this.

What we see, because of the structure and the randomization, is that only about 20 percent of those on the 24 week course were in this poor performing group whereas 50 percent in the 48 week were in this poor performing group.

So it's a very significant confounding. Have you looked at this for histologic response and have you looked at this for mortality? Is this core group that is genotype 1 and high titer viral load not only do they have a poor overall sustained virologic response rate, but do they tend to have a lesser

histologic response rate and a different toxicity profile and if so, then we have to look at the effects of intervention and in particular 24 weeks versus 48 weeks stratified by this factor and the analyses we've been presented aren't stratified by that factor.

DR. SIEGEL: On the safety analysis because of the 5 to 1 and 3 to 1 averaging out to 4 to 1 variations, there's a strong confounding particularly between high viral load, genotype 1 patients and the 48 week therapy.

DR. FLEMING: Absolutely.

DR. SIEGEL: They're very intensely enriched there.

DR. FLEMING: Fifty against 20.

DR. SIEGEL: And it's pretty hard to unconfound that. I think based on our expectations, we don't have high expectations that there are interactions for most of these adverse effects of interferon which are seen in diseases other than hepatitis where interferons are used, with the type of virus.

That said, we see, for example, three

times as many discontinuations and higher incidences of lymphopenia and neutropenia in a 48-week arm than -- does the data, can we use the data to tell us for sure that that's not because it was 48 weeks, but because it was 48 weeks rather than because more viral, more patients, genotype 1, high viral titer? We haven't looked at each of those possible interactions. In general, the numbers are small.

As far as the histology, you might start with a stronger presumption there that viral load or viral titer might well -- a stronger presumption that that might confound and impound histologic response. Certainly my priors would be stronger for that than for it impacting interferon associated with adverse events.

However, we haven't really made much of it because of the amount of missing data and the other issues discussed haven't made much differences in histological responses, so it didn't seem -- and the numbers are very small because it was only subsets who were biopsied or who were attempted to biopsy. So you start breaking that down, you can't -- you don't --

there's not much to look at.

DR. FLEMING: Jay, let me try to simplify this because basically what we're saying here is genotype 1 high titer, this is a separate group. It was identified to be a separate group when the study was designed. Separate both in terms of its predictiveness, i.e., they do less well and in terms of possible effect modification, the nature of treatment effect may differ.

The issue is if you ignore the stratification, the way the study was designed, there is a powerful confounding going on here because those that got 48 weeks, half of them were in this poor performing group whereas those that got 24 weeks, only 20 percent were in this poor performing group. As a result, when you look at the relationship of histologic response by these groups, you see no difference, no effect, whereas when you looked at sustained virologic response, you did see benefit in the 48 over 24 week at least in this genotype 1 group. And I'm arguing that it's a very simple analysis. You really need to carry this out, not only in

sustained virologic response, but for histology as well. There may well be a difference in histologic effect in the genotype 1 titer group and we just have to look at it. And for that matter, safety should be assessed that way as well because it could be that this is also confounding for safety.

DR. SIEGEL: Although this wasn't commented on, if we go to slide -- this would be in the FDA slides on histology, there's -- from the first study, as I was looking through these numbers, it's our slide 19. So the number who are intended to be biopsied --

DR. FLEMING: It's the second study that has this confounding though --

DR. SIEGEL: Right, but I'm making a different point here that's relevant to that point and I'll come back to it. So the numbers that were planned to be biopsied were 65, 110 and 110. If you actually -- if you look at the number of people who are planned to be biopsied, but who weren't biopsied, it's about 30 patients in each group including in the smaller group. So it's a much higher percentage of

patients in the monotherapy group who weren't biopsied, probably because they weren't getting good response and they were lost to follow up.

So my point -- so although that rate comes out at 72 percent compared to 76 and 80 and in fact, the histological response may well be much lower in that if you did it on an intent to biopsy basis as opposed to an actually biopsied basis, and I'm simply saying that the histological data are so complicated by missing data that trying to unconfound the balance and randomization is not likely to lead to any more meaningful -- and the numbers are so limited, to any more meaningful conclusions.

However, we will be glad to do that and --

DR. FLEMING: The point is to the extent that it's worth presenting it, it should be presented in an unconfounded way.

There's more to say, but time is short, so let me just move on quickly to the second issue and this relates to the first trial. By its design, it was targeting a 12 percent improvement and success rate of having achieving success and one of those

measures was sustained virologic response and we saw in monotherapy differences of 11 versus 8 and 15 versus 35, so 15 to 17 percent differences, nevertheless, the first trial was designed in comparing peg against Intron A. The target only 12 percent differences and we're told in the FDA document on page 8 that when much of the data was in hand on 815 patients, there was an interim analysis that led to a decision to power for smaller effects and hence use a much larger sample size.

Can somebody clarify exactly what information was in hand that led to that decision to power for even smaller effects when you were already powering for smaller effects in the first place, i.e., 12 percent than what you had seen in the monotherapy setting?

DR. HOFFMAN: I'm going to ask our statistician to respond. What I can tell you is when we initially discussed the protocol with FDA, they said, they suggested why don't you take a look because if you can show an 8 percent difference that would certainly be clinically relevant.

DR. FLEMING: Take a look at what?

DR. HOFFMAN: That's why I want to ask my statistician.

MS. LIN: What we did is -- FDA actually recommended us to try to power the study to look for a smaller difference. You are correct. Originally, we planned to detect a difference of 12 percent and we -- after we have about 800 patients data, four weeks viral data, PCR data, we did a sort of blinded look of the PCR data and then tried to increase the sample size to allow us to be able to detect a difference of 10 percent between the two combinations --

DR. FLEMING: So Amy, when you did this, did you have access then in these groups to what these results were by group, is that how you were --

MS. LIN: No, no. It's blinded. It's blinded. We are guessing ourselves.

DR. FLEMING: I'm very perplexed. What would have led to a decision to go for 10 versus 12 that you couldn't have made at the beginning of the trial?

MS. LIN: It was really based on the

recommendation from the FDA.

DR. FLEMING: Then why is it presented to us that this was a decision made at the time of this interim analysis? That could have been done at any independent point in time?

MS. LIN: Well, the decision actually was made after we had a discussion with the FDA and then we amended the protocol to -- adjust the sample size afterwards and it's based on the 4-week interim PCR data. So basically it's a blinded review of the available data.

DR. FLEMING: Let me try just one more time. With that 4 week PCR data, just very quickly, exactly were you looking at in those data?

MS. LIN: It is really looking at, I guess, just evidence of I guess response at that time point, using all available data and try to make a best estimate of the amount of additional numbers that we need to power the study at 10 percent.

So it's a blinded review.

DR. FLEMING: I'll go on, but that's -- you could have made the calculation of the numbers you

would have needed to power for 10 percent without looking at the 4-week PCR data, so the concern to some of us when we look at this is if it's a data driven change and sample size that has substantial ramifications on the validity of the statistical interpretations that you would do in the enlarged sample size and it's just very unclear to me exactly what you were looking at, because if it was purely an independent decision to power it to 10 percent which could be a valid thing to do, you don't need interim data.

MS. LIN: But we don't know exactly, I guess -- it's sort of guessing as well at that time point because we really don't know what combination arm will respond, but we do know from our monotherapy experience that what the monotherapy might have, so it's really a guess that we made at that time point.

DR. GULICK: We are going to have to wrap up soon.

Ms. Thiemann, you haven't had the opportunity to ask a question.

MS. THIEMANN: I'm sorry, thank you. I

have two questions unrelated to each other. The first being early in the presentation there was a statement made that there was ribavirin Copegus data that was outstanding and I was wondering how much was outstanding and would the receipt of that data affect what we've been looking at? That was in your presentation.

DR. SIEGEL: That was in reference to issues regarding manufacturing which we wouldn't bring to this table and would have no effect on the validity or interpretation of these data.

MS. THIEMANN: All right, thank you. And the second question is about the management of depression in the cohorts. There were so many patients that were dropped out for -- or that dropped out for neuro-psychiatric reasons and I'm wondering was it tracked the management styles of the clinician researchers that were investigating their groups to see differences in how many clinicians prophylaxed for depression in people who claimed that they were moody prior to starting their course of interferon? The only exclusion criteria were for people who were

seriously depressed, had serious depressive events and I know for sure that many people go in saying well, you know, I was down a little bit and sometimes I don't -- I'm moody and then clinicians will prophylax with antidepressants.

DR. HOFFMAN: Let me first answer that, the premature withdrawals for depression were actually quite low. This is from the 801 study. So most of the patients could be managed. What's confounded is that a lot of the patients were put on antidepressants even before they were depressed prophylactically. So it's hard to sort through it. But because of the low number of premature withdrawals, whether it was prophylactically or as part of treatment, it seemed to be effective and we certainly do agree that patients who were seriously depressed need to be taken off drug, need to be watched carefully, treated for their depression.

MS. THIEMANN: So have you looked at how many were treated prophylactically so we can try to understand going forward, maybe not for the basis of decisions that are being made today, but to be able to

make recommendations down the line, whether this is a clinical recommendation that could be?

DR. HOFFMAN: I'm going to ask Dr. Jensen what his experience is.

DR. JENSEN: I don't really have data from this particular study on how many were treated prophylactically, but in general, in clinical practice, if a patient has moderate to severe depression prior to entering the study, either they don't on to therapy if they have severe depression, if they have mild to moderate depression, typically will require a psychiatric evaluation of that patient to see if their depression is significant, should be treated prior to getting into the study and assessing their response prior to treating with antiviral therapy.

Once a patient with no prior history of depression shows clinical signs or symptoms of depression in a clinical study, I think the trigger that a clinician will use, will pull, at any one time, varies amongst clinicians. I think it varies tremendously from physician to physician in their

threshold to use SSRI compounds. Many physicians use it at very early -- any sign of depression and others may get psychiatric evaluation, a more formal evaluation to use those compounds in therapy. But I can't really tell you how many in this particular trial had prophylactic antidepressant therapy.

DR. GULICK: Okay, every one on the Committee has had a chance to ask questions. I'll actually ask a question myself.

This is regarding the relationship of neutropenia and serious infections. Can you remind us what the definition of a serious infection was on these studies?

DR. HOFFMAN: Yes, serious infection is like any serious adverse event is an event that requires hospitalization, generally. It could be hospitalization or prolongation of hospitalization. It can be, remind me, Jonathan of all the different things. Our safety expert, you --

DR. SOLSKY: Actually, it involves both the hospitalization prolongation of the hospitalization or in the mind of the physician

himself he feels that this is clinically significant and above and beyond a standard type of infection. He will indicate to us that he considers it serious, even though not necessitating hospitalization.

So that also would be considered serious infection.

DR. GULICK: Do you have a list of the specifics, serious infections?

DR. SOLSKY: Yes.

DR. GULICK: From the study, I guess we only saw the totals.

DR. SOLSKY: Right, we'll just have to pull that one up.

And we can also show you, if you're interested the pathogens that were involved in those cases that they were isolated. This is from our first trial, 801 slide up, please? This is the entire list of types of infections. You'll note that any particular type of infection was reported relatively and frequently 1 to 2 cases in either of the Pegasys Copegus or Rebetron arm.

And in terms of the particular pathogen,

slide up -- you can see actually the majority of the cases, the 16 cases, we did not -- were not able to isolate a pathogen and in fact, the reason you see this presumed bacterial is because the patients received antibiotics because of the infection itself and no pathogen was isolated.

DR. GULICK: Did I understand correctly that ANCs at the time of the infections are unavailable?

DR. SOLSKY: Well, ANCs at the time of infection, obviously these are patients who are hospitalized, so these were admitting labs. So that's the reason why we show in our analysis the ANC pari-infections to be able to capture that from our data base itself. For particular types of infections, yes, we do have that particular information. For example, the case of the staph aureus epiglottis that was brought up anecdotally. We have for that particular patient who prior to the infection, we can actually bring that one up, who had a PMN, ANC, actually of 1600 prior to the infection itself, came symptomatic. Could we please bring up this one? I

think this one is sort of -- this is actually the case that the FDA has presented to you and it's the case of oxacillin resistant staph aureus epiglottitis.

As you note, the patient ends up having on Day 33 pain on swallowing and two days later, fever. Prior to that their platelet count from baseline, as you see, the PMN at baseline was 2900 and about a month after they were around 1500. As the infection begins, you can see that there's a decrease in the ANC as well as in platelet count and only at this point is the patient actually hospitalized and starts to receive antibiotics. So there's a course of about two weeks of a process going on where apparently the patient had not been treated and during that period of time this confounds, actually, the decrease that we initially saw prior to the infection where the patient was.

DR. JOHNSON: But you're not seeing fungal infections and the scary stuff like p.sariosos and -- I know they have prescribed antibiotics, but were they culture for fungus?

DR. SOLSKY: I can't say specifically in

terms of all of these cases. I know some of them had a very thorough workup and we did not identify any cases of fungal infections. In fact, as I showed you both in this study and we also can show you that for our 942 study, the common pathogens were actually staph, strep and e.coli consistently. We didn't see any kinds of infections that would be associated with an immuno compromised host.

DR. GULICK: One last point on this, did I understand correctly that only one person in both studies had their physician administer GCSF?

DR. SOLSKY: That is correct.

DR. GULICK: And can you explain that, given the amount of neutropenia that you saw and the availability of these drugs and the fact that they were not excluded on either study?

DR. SOLSKY: Well, in cases where the patients may have been withdrawn, then subsequently -- actually, that one case where the patient did receive GCSF that the patient was withdrawn and then received the GCSF.

In the other cases, the patients

apparently were able to be managed just by dose modification.

DR. GULICK: So on the studies it was obviously much more preferable to the investigators to take away these drugs than to add growth factors, clearly just from the numbers.

DR. HOFFMAN: Temporarily, the other thing is we took out a slide that you had in the presentation up until a few days ago which shows the time course and what happens is there's an initial drop in the neutrophil count during the first two weeks and then there tends to be a stabilization. So patients tend to drift downward. So someone who got -- and Grade 4 neutropenia was only present in about 4 or 5 percent. Most of what you've seen up here were grade 3 where you wouldn't treat it. So they get there and they dip below 500. The investigator adjusts the drug and then they come back up. And I think that's it, except for these unusual cases where somebody had an infection and where the neutropenia is likely due to that more than the drug. They tended to get there slowly and so you could dose reduce as you

saw them going and they came back up.

DR. GULICK: Okay, we're running over. Two people have -- make that three. Dr. Siegel?

DR. SIEGEL: Just a quick comment to say that what we know about the relationship between neutropenia and infection risks comes predominantly from chemotherapy induced neutropenia, some from bone marrow transplantation, but very little data or limited data, not very little, from HIV and other issues. And it's worth noting a couple of differences. One is that neutropenia in patients on interferon, the time course is likely to be different. Instead of a sharp very low dip, it's not when it reaches 400 that the next day it's likely to be 100, as you might see in chemotherapy, but it's also true that chemotherapy, most chemotherapy used -- have important mucosal effects which may increase the risk of infection, time courses, just a number of differences.

On the other side of the coin and I think what Dr. Tauber was trying to note, is that interferon has a number of functional effects on a number of

aspects of the immune and inflammatory system. And so we don't know whether patients who are reduced to 800 or 1000 in this setting may or may not have normal phagocytic function or whether those who are under 500 don't. So just wanted to highlight how beyond certainties on both ends of the coin.

DR. GULICK: Thanks. So Drs. Hoofnagle and So were the last two people to have questions.

DR. HOOFNAGLE: Very quick question. You mentioned the 10 women became pregnant, three who were on drug. Could you tell us about those three? Did they have abortions or did they end up with normal babies? Some of the women ended up with a normal baby.

DR. SOLSKY: In three female patients, what they ended up having was two of those had an elective abortion, one had a normal baby.

DR. HOOFNAGLE: Had a what baby?

DR. SOLSKY: A normal delivery and a normal baby.

DR. HOOFNAGLE: Very lucky. My other question was in your previous studies you always

combine cirrhosis with 3 plus fibrosis. Here, you kept saying cirrhosis. Do you actually mean those people actually had cirrhosis that you didn't combine bridging necrosis with cirrhosis?

DR. SOLSKY: We combined transition to cirrhosis with cirrhosis, the reason being that our consultants told us that patients have transition to cirrhosis, it's likely they have cirrhosis in the liver.

DR. HOOFNAGLE: What is transition to cirrhosis? Is that a 3 plus?

DR. SOLSKY: Generally yes.

DR. HOOFNAGLE: And did you have a single pathologist, one pathologist do all this or was it local?

DR. SOLSKY: The admission biopsies were done by local pathologists. When we had the prepared biopsies, those were centrally read.

DR. GULICK: Dr. So, the last question?

DR. SO: I was very pleased to see the Asian patients responded very well.

(Laughter.)

It is because of the genotypes or other reasons?

DR. HOFFMAN: That's a good question. The numbers are very small. Most of them came, I believe, from Taiwan.

DR. SO: You actually have more Asians than African Americans in the study.

DR. HOFFMAN: Yes.

DR. SO: And the other question is I have this -- when we look at sustained viral response from the FDA table trial page 15, looking at that data it seems like at 48 weeks that is after the end of treatment was -- the sustained viral response rate was 68 percent and in the ensuing 6 months it dropped to 47 percent. And then the biochemical response, however, remains almost the same, 54 percent to 50 percent. Do you have any further data like 9 months or a year after treatment?

DR. HOFFMAN: I'm not sure what you're referring to.

DR. SO: I think this is from the FDA data from -- looking at your 48 weeks. It's Table 12, page

15. And there it lists your viral response at Week 48.

Right at the end of treatment. The viral response at that time, undetectable HCV RNA was 68 percent, but then at 72 weeks it dropped to 47 percent. So at the end of 48 weeks, in the ensuing six months, 30 percent actually relapsed. So this seems like much higher than Dr. Hoofnagle was referring to. So I was wondering if we are using sustained viral response as the key indicator for assessing this drug, compared in the past only a couple of months ago we were here looking at ALT and --

DR. HOOFNAGLE: That's the end of treatment response. Forty-eight weeks is end of treatment response. Twenty-four weeks later is sustained response.

DR. SO: In that period of time, 50 percent relapse, I was wondering if you followed these patients out longer, would there be more patients who would relapse?

DR. HOFFMAN: No, as I mentioned before, in combination therapy as well as monotherapy, we

follow patients out up to four years. Combination therapy a little less because it's earlier, but 19 percent of the patients who are sustained responders, that is six months later continue to have undetectable virus and most of the relapses actually occur at about week 8 to 12 and then you don't see any subsequent relapses.

DR. SIEGEL: We actually have a lot of follow up data from various interferon trials over the past decade, decade and a half and before the combination regimens as many as 50 percent of patients typically would, if you call it relapse, we don't call it -- I guess we don't consider it a response until after those six months of therapy.

Almost all and in the variety of studies where we have data, almost all -- you see most, as you've heard in the first three months, you see a significant number in the second three months and you see very few after six months and that 50 percent number, with the combination regimen has been lower, so you're observing the 30 percent is actually less than what we had seen for many years with interferon

monotherapy.

DR. HOOFNAGLE: I think these numbers are incorrect, actually here. The numbers on page 15 I think are incorrect.

DR. GULICK: Okay, perhaps we can look into that over the lunch hour.

In my haste, I have forgotten one member of the panel who has been patiently on the phone all this time, Dr. Stanley, do you have a question?

DR. STANLEY: In the interest time, Trip, I believe most of my questions have been answered. So I will save you some time.

DR. GULICK: Thanks for hanging in there. So we're going to break for lunch for 50 minutes, which brings us back at 20 of 2. Thanks.

(Whereupon, at 12:51 p.m., the meeting was recessed, to reconvene at 1:40 p.m.)

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

1:49 P.M.

DR. GULICK: Okay, welcome back from lunch, everybody. I'd like to call to order our meeting of the afternoon and we're going to start with the open public hearing.

I'd like to open the open public hearing part of the meeting. There are actually two people that signed up. We're going to flip their orders because one has a slide presentation that's being put together right now, so the first speaker is Mr. Jules Levin, who I don't actually see.

Jules, are you here? There he is.

Jules, we'll give you a minute to get your stuff together.

The second speaker is Dr. Brian Murphy, and as I mentioned, we're just putting some slides together for him, putting his slides together for us.

Would you like to speak from up here? That would be great. So this is Mr. Jules Levin from New York, representing NATAP.

MR. LEVIN: I thought there were three speakers before me, so I thought I had a chance. I

saw I was fourth on the list.

Hi, my name is Jules Levin. I'm the Executive Director and Founder of the National AIDS Treatment Advocacy Project. It's a community-based organization in New York City and we do, amongst other things, treatment education in New York and all over the country and we have a Ryan White Grant to do that in New York and federal support to do that and this year we've provided coinfection and hepatitis C treatment education in 12 cities throughout the United States.

I've had HIV for 19 years and probably hepatitis C for 25 years. Just finished therapy with pegylated interferon and ribavirin myself and had an end of treatment response of undetectable. Still waiting for my sustained response. So I just have a few points to make here today.

Well, the first thing I want to say I speak for myself and I think I speak for the broad community of people infected with hepatitis C as well as coinfection with HIV and hepatitis. Everybody is very anxious to have this application approved for

combination of Pegasys and ribavirin. But you know, everyone thought it was a done deal before the hearing We thought that Crixavan seven years ago and Ritonavir were done deals and the vote on the Advisory Panel was very close in approval of Crixavan. It was something like 8-5. And Ritonavir they had to hold over until the next day to get it approved. So I'm not sure that there's anything like a done deal with any Advisory Panel, no matter how obvious it should be. Could you imagine if we didn't approve protease inhibitors seven years ago?

The Advisory Panel didn't want to approve HIV viral load testing shortly after that and I pointed out to the Advisory Panel, you just approved three protease inhibitors based on viral load changes, but you don't want to approve viral load.

So nothing is a done deal, but I want to say that the community feels that this application should be approved and that the Panel should recommend that to the FDA. And that the FDA should approve it.

I want to raise a few issues that may not be a part of the decision today, but really need to be

aired a little bit, issues that people know about anyway and I'm not sure what the answers are either, but really need to be brought to people's attention. The drug companies, the NIH, the FDA and researchers and doctors and to the audience to people from the news business, people who write articles for magazines and newspapers, as well as the drug industry out there in the audience.

I'm really concerned about the hard to treat populations. Sure, it's easy to say we need new drugs. These drugs have pegylated interferon or ribavirin has effectiveness over and above standard interferon and it's easy to say we need and there is development for new drugs to make therapy better, but in the meantime, what are we going to do with hard to treat patients, nonresponders, who are not responding that great, previous nonresponders who are not responding that great to the pegylators? Some of them are responded, the rates, the preliminary rates are about 15 percent of previous combination therapy nonresponders to maybe 20 percent on average are responding to the pegylated interferon and interferon.

But what are we going to do with them? And it's not just the nonresponders, but people with coinfection, HIV and hepatitis C, 80 percent of them have genotype 1 and as was brought up here, well over 90 percent of African Americans have genotype 1. What are we going to do with these individuals?

And I'd like to see some studies with the current therapies to try and improve the response rate.

There are a couple of things that have come out recently at the recent AASD liver meeting, such as dosing the first couple of days with standard interferon and then immediately start on the pegylated right after that or dosing the same together where you have higher levels initially of drug may improve the sustained response rate. And there was some data on this at the conference suggesting this may work.

There's also some data using double the dose of one of the pegylateds. There was a study presented that looked like it improved the response rate. We need to explore this because there are a lot of people with coinfection and there are a lot of

nonresponders who have vast disease and they don't have the time to wait for the new drugs and we really need some studies and I'm not just pointing the finger at the drug companies here, I'm pointing the finger at the NIH and at the CDC and the FDA.

Where is the funding for testing and prevention for hepatitis C like we have for HIV? Where is the funding for testing and prevention, the money for hepatitis C in the HIV positive community?

We have money coming out the kazoo to do testing and prevention to fund CBOs, community based organizations, to do street testing and so forth for HIV, but where's the money to do that for hepatitis? There is no resolution here on the part of the CDC, as I see it, to do it and I point the finger at the NIH too. Where is the money to do this? Where is the resolve to do this? I don't see it at all.

Another point that was brought up and how come the mainstream press isn't writing about this because it's not sexy? That's what I think. Reuters, Bloomberg, I don't see them writing about this very much.

There was mention here and I really -- I was going to mention it, but it was brought up by some of the panelists. We need long term data. I do believe that the surrogate data is meaningful in hepatitis C. But I think we need some long-term studies and to evaluate the long-term outcome of surrogate data and I think Jay Levy mentioned how hard it is to put together such studies. Despite that, I think we really need to look at this and consider this because we as patients and isn't this what this is all about is the patients? Isn't that what it's supposed to be all about? Let's not forget that.

There isn't enough data to go out 30, 40, 50 years to show the final outcome of efficacy of these drugs and we really need to consider doing that.

Lastly, I just want to mention that the gaps in reimbursement for treatment and diagnostic testing for hepatitis C, there are tremendous gaps. The ADAPs are not covering this for the most part. There are gaps in public reimbursement as well as private reimbursement. The problem is that the gaps in public reimbursement affect tremendously HIV

infected individuals who have coinfection because the HIV community depends on the public reimbursement system and so what's going to happen in the short term in terms of accessing treatment with pegylated interferon and ribavirin if you get your coverage through ADAP. And I understand the crunch, but we've always had a crunch with everything and I think that we need to pry up some money here to put towards people with hepatitis and people with coinfection.

Let's get some money loose from the government here, from HIV a little bit and put up some extra money for coinfected people for education, for treatment for testing, for prevention, for diagnostic tests. We need some money for this and I'm not sure I have the right ears in the room here today, but maybe if I'm lucky some people will talk about it a little bit.

We had a meeting with the administration last week where we talked about this. They promised they would do something about it. Maybe that will help a little bit.

Okay, thank you.

DR. GULICK: Thank you very much. Are we set to go with one minute on Dr. Murphy's presentation.

Our next speaker is Brian Murphy, Dr. Brian Murphy from InterMune, Incorporated.

(Pause.)

DR. MURPHY: Thank you, Mr. Chairman, Members of the Committee and members of our audience, I want to thank you for this allotment of time to speak today. I'd just like to preface my statement with the following that these slides and the data and the questions submitted on these slides were submitted to the FDA Advisory Committee prior to the release of their findings and so some of the questions posed today by me may have been already addressed. However, I think there are a couple of key points, little nuggets in there that may be useful to look at.

In accordance with the rules put down by the Advisory Committee, as far as disclosure is concerned, there should be known that I presently serve in a corporate capacity with InterMune. InterMune is a biotechnology company that develops

drugs within the HCV therapeutic area, including an array of interferons to treat this disease.

I guess prior to the release of the FDA Advisory Committee findings, information that was still pending for the U.S. treating community were essentially what were the absolute number of U.S. patients in the Pegasys ribavirin registration trial, the withdrawal rate for the U.S. versus non-U.S. or ex-U.S. patients in this trial; the percentage of response of U.S. versus ex-U.S. patients enrolled in this registration trial, and the safety profile of U.S. patients versus patients outside the United States.

Certainly up until this meeting, the data publicly available had to do with data published in the New England Journal. In that journal, the paper quoted a response rate of 56 percent and because they did not count 28 patients that did not receive a first dose that analysis was more of an on-therapy analysis and actually within that paper looked at data points from Week 68 through 72 of treatment.

Also prior to this, this drug had been

approved in the European Union and the analysis by that regulatory authority actually issued two response rates. One, the 54 percent response rate was basically an on-therapy analysis and used data from Week 60 carried forward. The 50 percent analysis was an intent to treat analysis and according at least to that regulatory body posed a borderline statistical significance versus the comparative group.

So essentially up until this time, these were the numbers that treating physicians had access to. However, both the data from the New England Journal and from the EU naturally did not go into specifics of U.S. response rates.

Based on the New England Journal article, the total number of patients were 453 and those that completed follow-up were 334. The number withdrawn for insufficient response and I believe in that paper was 24 weeks were 34 patients, leaving about 85 or 19 percent withdrawn for other reasons and of course, this rate, this 19 percent rate based on data that was presented this morning, is somewhat higher than what was seen and I guess it all depends on what the

definitions used are that will explain that rate.

The EU discussion and I apologize, these are not numbers specifically stated in the EU, but computed by statistics given in the EU, had some different numbers, total number of patients, 468; 337 who completed follow-up and this is based on a 72 percent rate. And the number withdrawn for insufficient response was 35 and 96 withdrawn for other reasons and that was based using the percentage rate given in the New England Journal article. So the EU discussion really did not go into as great of an analysis of why patients withdrew as the New England Journal article.

The first two bullet points on this slide might be a little moot, given the FDA data presented this morning. With the 10 percent, 10 to 11 percent withdrawal rate, based on the FDA analysis, certainly that rate does not exceed the rate that you see in studies. However, what would be interesting to know is what was the absolute number of American patients that withdrew from the study? And based on that withdrawal rate, is the baseline American presence

within this registration trial more diminished by the withdrawal of U.S. patients?

Looking at geographic response and looking at treatment response based on geographic location, there is precedence for this. An FDA Advisory Panel did look at this for another pegylated interferon, interferon alfa-2b and of course, in that analysis the U.S. response rate was found to be lower as was the Rebetron or Intron A ribavirin combination therapy. So there does seem to be some background where Americans do not have as high a response rate as non-Americans.

It may be indicative of the makeup of the study populations. Data from the CDC shows that at least there's a preponderance of African Americans and Mexican Americans and people of color with hepatitis C and as was pointed out this morning on study demographics, only about 5 percent, 5 to 6 percent of the patients in the registration trial for this drug today were African American and delineation as far as Mexican Americans were even lower with actually more Asian Americans represented in the study group.

What's interesting to note is that if you look at the demographics of HCV infection in the United States, they mirror that of obesity in the United States. African Americans, according to NHANES data show a rate of obesity four times that of Caucasians and Hispanics also show a rate of almost 3 to 3.5 times that of Caucasians. So it is interesting that when you look back at the hepatitis C demographics and the obesity demographics in the United States, there is overlap between those groups.

So I think it is important to possibly address is there a weight-based component to this and I know that there have been some analyses conducted, looking at the impact of genotype, but I did not see a slide in the presentation this morning and one that may be interesting to look at is a slide looking at the genotype 1, high viral load patients in both the U.S. and non-U.S. and see what those response rates are. Is there a difference between those response rates, as well as genotype 1, U.S. versus ex-U.S.

Certainly once the data is collected and analyzed, we are supportive of intent to treat

analysis and we were happy to see that analysis this morning fit this analysis. Certainly intent to treat analysis is something that you see with varying prevalence in the published data, sometimes published data will actually say that the studies are intent to treat, when they are in fact on therapy analyses and so intent to treat should include all patients who are randomized, in the hopes of avoiding comparing non-randomized cohorts.

Certainly for the treating community, similar centers are used and they're certainly between the peg interferon alfa-2a and 2b. There is significant test center homology for lack of a better word, a lot of the same centers are used for those studies. Then they're drawing from the same patient populations and so by having an intent to treat versus an on therapy analysis, certainly helps physicians and their patients look at data a little bit better, even though there is no head to head comparison. Certainly we support the guidance for industry as put down by CBER that intent to treat provides estimates of treatment effects that are more likely to mirror those

observed in subsequent practice.

We're happy to say that at least in published data, Roche also supports the use of intent to treat. In a paper published by Roche, "What Clinicians Need to Know", they comment the intent to treat analysis includes all patients assigned to each study group, regardless of whether they're dropped out of the study or switch therapies. On treatment analysis includes only those patients who completed the study within their originally assigned groups. Therefore on treatment analyses failed to account for drop outs and switches and their treatment success rates tend to be deceptively higher than those seen from a similar ITT analyses and we wholeheartedly agree.

So as far as conclusions are concerned, global trial results may not be reflective of the American experience and bottom line whether it's weight, whether it's genotype, whether it's viral load, patients do have to go in -- American patients do have to go into an American physician's office and treatment decisions are made and it might be good in

the interest of consumerism for the Agency to publish the American response rate so that patients and physicians alike will have a better idea of what the realistic chances are for a therapeutic response.

For informed treatment, we urge the following American data would be valuable to know and as I mentioned before, this has been covered somewhat this morning. The absolute number of U.S. patients in the study, U.S. versus ex-U.S. response rates, safety parameters and withdrawal rates.

In conclusion, we would also like to adequately compare the data. We are in complete agreement with the ICH guidelines that support the use of ITT analyses and agree wholeheartedly with the Roche position that data analyzed by other methods may lead to deceptively higher results.

Thank you very much for your time.

DR. GULICK: Thank you. Are there additional people who would like to make statements at the open public hearing that have not signed up to do so?

Okay. Seeing none, I'll go ahead and

close the open public hearing part of the meeting.

We'll turn now to the charge to the Committee for questions and discussion.

Dr. Weiss, you want to charge us?

DR. WEISS: Actually, I don't really have any specific charge other than we have developed a series of questions with some background to provide some context for the question and we just look forward to a discussion of all these issues.

DR. GULICK: Okay, great. So if the Committee Members could actually bring out the questions to the Committee and there are nine of them. I'm going to try to keep us on time because I know several people mentioned that they have planes to catch.

So let's just jump right in. I'll go ahead and read these for everybody for the audience members too who may not have a copy.

The first question, pegylated interferon and ribavirin dose optimization. The dose of pegylated interferon used in the combination study is 180 micrograms, fixed dose administered once weekly

subcu with selected based on monotherapy studies. No dose ranging studies of Pegasys in combination with ribavirin were carried out. The selection of the ribavirin dose was based in part on its similarity to the so-called Schering ribavirin or Rebetol. In Study 1, the Copegus dose was crudely weight adjusted. As we heard, 1,000 -- if you weigh less than 75 kilograms, 1200 milligrams for 75 or greater, administered in a split dose, once daily with food.

Study 2, two doses of ribavirin were compared, a low dose of 800 milligrams and then in addition the crudely weight adjusted dose.

Exploratory analyses suggested that individuals treated with combination therapy who were greater than 85 kilograms had a lower SVR than those who weighed less than 85 kilograms and experienced less toxicity, particularly hematologic compared to patients with a lower body weight.

So focusing on dose optimization, Question 1 to the Committee: should the sponsor evaluate lower doses of pegylated interferon, for example, 135 micrograms and/or weight based dosing versus fixed

dosing of Pegasys in combination with Copegus?

Dr. Wood?

DR. WOOD: I have a request of the FDA because in their slides the SVR response stratified things by 85 kilos, but the toxicity responses were stratified according to a cut off of 65 kilograms. So it would be useful to see the toxicity parameters also expressed in 85 kilograms so we could be comparing apples and apples because slides number 31 and 57, again, the cutoff was 65 and then for the SVR for both 801 and 942 studies, slides 22 and 43, the cutoff was 85 kilograms.

DR. GULICK: Dr. Siegel?

DR. SIEGEL: Well, I actually inquired of the Committee, of our Committee why they were represented that way and the particular reason they are presented that way is to highlight, to specifically look at the lightest patients in terms of addressing the concern as to whether there was unacceptably high levels of toxicity in the lightest patients and similarly the potential for substantially lower toxicity in the heaviest patients.

It's my understanding that weight works as a covariant across the board and that the differences based on where you choose a cut point probably don't matter, but I can't speak to that. I don't know, have you looked at a variety of different cut points on weight?

DR. GULICK: Can you tell us why you used 65 kilograms?

DR. TAUBER: The 65 kilograms was selected basically because it was -- I was looking for a range. the 85 kilograms represent 10 kilograms above the 75 milligram cut point where the dosage is increased and 65 by symmetry gave me another section that was 10 kilograms less. It was just an empiric choice.

DR. GULICK: I would just echo what Dr. Wood said. It's challenging for us to try to evaluate this with three different cut offs being used, one for SVR, one for weight and then one for dosing of ribavirin.

Yes, Dr. Alter?

DR. ALTER: I don't know that I really know enough or have enough information regarding the

weight-based issues in that these cut offs sort -- or at least the 75 and 90 -- the 85 kilograms represents probably what a 5'10", 5'11" male might weigh if he was of normal weight and they're all very high or both 75 and 85 would be high for most women. Then you have to take into account genotype. Do we -- it seems to me that we have to look at this based on genotype as well as gender. I don't know how -- I don't see how you can make one -- I mean these are not really -- these are average weights. These are not particularly high weights for men anyway. So I'm not clear as to what it is -- what we're trying to achieve by doing -- by exploring lower doses since --

DR. GULICK: Dr. Kumar?

DR. KUMAR: I actually have a question to ask before I can think through this question and that is the Agency had presented data based on lab abnormalities by weight and by BMI.

Do we have similar data for depression based on weight? Because I want to preface my question because when I think about it as a clinician, the lab base of neutropenia, anemia, I have factors to

help me with that, but depression, as already has been pointed out, was not actively asked for.

We know as clinicians that few patients actually volunteer whether they're depressed or not. It takes much skill in the clinical setting to elicit early depression. By the time they're suicidal that's different.

So I'd like to know was there a difference based on weight, on effective depression?

DR. GULICK: Dr. Tauber or Dr. Siegel?

DR. TAUBER: We did not look at the depression. We chose the hemoglobin of less than 10 and the neutropenia because they were objective laboratory values that were more amenable for analysis. We did not actually address depression as a --

DR. ALTER: Can I -- I'm sorry, can I follow up because it's about the same --

DR. GULICK: Sure. I just wanted to let the sponsor have a chance to answer that same point. If there's any data available about weight based and the occurrence of depression.

DR. HOFFMAN: We looked at AEs, all AEs in patients according to body weight. I believe we looked at was it less than 65, 65 to 85 -- do you have it, Dr. Solsky?

DR. SOLSKY: Could I have that slide up, please?

We looked at adverse events and we broke them down in less than 65 kilos, 65 to 85 kilos and greater than 85 kilos. And to make this slide somewhat reduced in size to be able to read this, we just put in those events that even suggested that there might be differences in groups and we tried to find consistency.

So looking at these events, one notes actually that the only difference that was noted in terms of adverse events that occurred frequently at the lower dose range was alopecia, asthenia, UTI and menorrhagia. As you can imagine, these are events also that when you look at by gender you find these same adverse events. So it's confounded by gender.

To answer specifically your question of depression, because it does not appear on this it

means that they were the same, basically, in the lower than 65 and in the other ranges.

DR. GULICK: Dr. Alter, follow-up?

DR. ALTER: Yes, let me reword the question. Given the question that the FDA has posed, what is it that you would want to achieve with different dosing, what different endpoint would you want to explore?

DR. SIEGEL: That is a question to the FDA, yes?

DR. ALTER: Yes.

DR. SIEGEL: We are certainly not asking for a risk benefit assessment as to whether this should be given by weight base dosing as there are no data giving it by weight base dosing. Rather, I would frame, and as some of you know we've had extensive discussions on a related, closely related question regarding the -- at the meeting a year ago regarding a different product.

The product was only studied in a fixed dose regimen. We were told at this meeting that the rationale for that involved data regarding the

clearance although clearance hardly alone makes a rationale for a fixed dose. A drug can have -- many drugs can have the same clearance in larger and smaller people, but they have different volumes of distribution and get higher levels in smaller people. I don't want to go into all the PK, but there's a strong presumption whether it's broad variations in patient size that there will be variations in patient levels and that large people will experience less drug. These analyses on this, as they did on the other product suggests lower response rates in larger patients and higher toxicity rates in smaller patients. There are a number of explanations to that, including the possibility that smaller patients are being dosed more intensively than larger patients and so the question before the Committee is whether that's something that ought to be looked at by further dose ranging and particularly looking at weight-based dosing.

DR. GULICK: Dr. Sjogren.

DR. SJOGREN: Thank you. The way I understand the question and I think it's based on the

data that Roche presented this morning in which when they looked at Pegasys monotherapy, 135 and 180 micrograms, they end up with exactly the same sustained viral response at Week 72. And so the question is can we get away with 135 micrograms instead of 180 and therefore reduce side effects that with the higher dose of medication can be seen.

I think that's a very fair question and moreover, when Roche presented Slide 22, they said that adverse events were indeed less, were 21 percent with 135 micrograms and 27 percent with 180 and they went on to speculate that although there is a delta there and it's a slight increase with 180, that the reduction doses will be 90 and 135 and the 90 micrograms are not -- are suboptimal. And that may be true, but I don't think it has been tested and I think it is of importance that we evaluate such a dose because obviously if we can get away with less, maybe it will be a cheaper drug for our patients. That would be very good. That is one point of view that I have.

Another one is the FDA in the packet that

they sent to us have in the baseline characteristics in Table 4 a number of weights, less than 64, less than 74 kilos and so forth and so on, but I haven't seen in the presentation either of the FDA or of Roche what sustained viral response were achieved by those weights and I think that is paramount for us to be able to answer the question as correctly as we can. Should we be asking Roche to look at weight dose Pegasys? You know, when I think about it, I think 180 micrograms sounds wonderful. It's very easy to give and what not, but 180 micrograms for a woman of 50 kilos and for a man of 90 kilos may not do the same job and I think we have the data looking at us. I mean the data is somewhere and maybe the data can be produced, would be very good.

And the last thing I want to say about this question is that I really don't know anything about Copegus and I am a little bit uncomfortable that this is the ribavirin. I think I have to take at face value that the FDA is looking at it for bioequivalence, but if we are being asked questions about it, I don't know because I haven't looked at any

single bit of data that shows to me that it is bioequivalent to the Rebetol that we have grown accustomed to use.

DR. GULICK: Can the Agency address the third part?

DR. MARZELLA: I'd like to follow up on the point that the Committee Member raised about --

DR. GULICK: Speak into the mic, please.

DR. MARZELLA: I'd like to respond to one question that the Committee Member posed about the data on virologic response and body weight. That data is in Appendix 1 on page 59 and it does show that numerically with increasing body weight that the sustained virologic response decreases and in particular in the various treatment arms.

DR. GULICK: Can someone from the Agency address Dr. Sjogren's concern about Copegus, the ribavirin preparation?

DR. SIEGEL: Perhaps one of my colleagues from the Center for Drugs could, but let me -- good, excellent.

Let me clarify so I understand the

question. You're asking, you're saying your answer to whether Roche should study their ribavirin will depend on how similar it is to Schering's ribavirin because you may think that the data -- from what you know already from Schering may impact what you think Roche needs to know about their product. Is that right?

DR. SJOGREN: Yes.

DR. REYNOLDS: I have two points to make. First, the two products are bioequivalent. We did review that and Roche's product and Schering's product are bioequivalent.

But on the two pivotal clinical trials were not conduct with Schering's product. They were conducted with the product from Roche. So that's where the safety and efficacy data come from, but they are bioequivalent.

DR. GULICK: Dr. Sjogren, let's focus this because this question is two questions and I'd like to take each one separately.

I know some people have said they want to speak, but let's take the very first question. Should a lower dose of 135 micrograms be studied? Let's just

consider that for a moment. And Dr. Sjogren started us off.

Dr. Sun?

DR. SUN: I know we want to get to the answer of the question, but I would like to come back to a point that Dr. Englund made this morning which was the dose modification data is very important here because fully a third of the patients did modify their doses. Now the sponsor makes a good point that that includes people that may have just missed a single dose, but it also may include people that had significant and sustained dose reductions and I think it's important to point out that that percentage is pretty large compared to the margin of efficacy that we're seeing particularly in the 801 trial.

So I think we can make a better response to the first couple of questions actually which all relate to dosage. If we understand this dose modification data because that, to me, is a surrogate for toxicity and I think that's why we even have the question being posed here.

So I think that it would be very helpful

for us to understand qualitatively a little bit more about dose modification, so if there are any analyses that have categorized how much people dose reduce, I know the FDA did an analysis where they analyzed from the efficacy standpoint the cumulative doses that patients had received, so you must have looked at -- certainly have looked at it from that angle. But I think the more important question is what is the relationship of dose modification to weight? So of the patients that did reduce their dose were they predominantly lighter people because that may signal something in terms of the drug exposure and then because you're giving two drugs, one of which is crudely weight adjusted and the other which is not, it's a pretty complicated analysis, but I think what you also want to do, therefore, is look at dose modification from the standpoint of interferon dose as well as interferon weight adjusted, weight-based exposed and do the same thing with ribavirin because you need to tease the two effects apart. And in the sponsor's presentation, I believe on slide 14, there is an analysis of the ribavirin weight based exposure

and it shows this sort of jagged pattern because there's a cut off at 75. So that provides some opportunities to analyze the data with comparable weight cohorts. So I know that's a lot of data to look at, but I think ultimately if the question is should we ask the sponsor to look at a lower dose, you have to have a hypothesis and a hypothesis that seems, you know, reasonable to test is that toxicity is driven somehow by drug exposure and I don't think we've shown that either way.

DR. HOFFMAN: May I show a slide?

DR. GULICK: Sure.

DR. HOFFMAN: We are specifically addressing the question here about whether a lower dose, 135 is associated with a safety savings and patients specifically less than 65 kilograms which is, I think, the group that is under discussion.

And what we see here, this is from the study that evaluated monotherapy 135 versus 180. If you'd like to see ribavirin data, we have ribavirin data as well regarding weight and response and safety. However, all AEs, not surprising, are very similar.

Serious AEs, essentially the same; grade 3-4 neutropenia, 58 versus 52. Dose modification, you specifically asked about what the dose modifications were. AEs or labs; AEs themselves, neutropenia, thrombocytopenia, very similar; premature withdrawals, somewhat higher in the 180. But dose modification is essentially the same.

DR. GULICK: So in follow up to this, I guess the reason that this is being proposed is this is from your monotherapy study, right? So the question is could you get by with a lower dose of pegylated interferon with ribavirin and therefore achieve less toxicity and has that been looked at and the question to us is would it be a good thing to look at?

DR. HOFFMAN: There are a couple of ways to go on this. One, I did show the slide of the 80/80/80 suggesting when you start to back off, now that's three different things that could have happened there. I could have been the Pegasys, it could have been the Copegus and it could have been the duration of therapy. But when you impact those, you do lose

efficacy. Genotype 1, particularly, we're concerned, and that's why we raise the issue about when we move forward and monotherapy 180 is our per dose and this information was reviewed by FDA and was thought to be appropriate for 180, I would add, that we went ahead with 180 based on the interim results and based on the histology. We are very concerned about losing efficacy.

One possibility is to shorten the duration of Genotype 2-3 and look at shorter duration because we know if we retreat those patients and we have data and I can share it with you, it's that ASLD, that if we retreat patients who receive 24 weeks of treatment and we treat them with a full course, that they response with responses very similar to the naive patients.

If you lower the dose of Pegasys because of the interim virological results, we're concerned you're going to lose people instead of getting them as responders who might relapse, they're nonresponders, relapses we can treat. Nonresponders, we don't do very well in.

DR. GULICK: Thanks. I'd also like to pose this to the Committee. Dr. Sun asked for a hypothesis and as I'm interpreting what I'm hearing, the hypothesis or what we know is that we haven't seen data with a dose of 135 micrograms of Pegasys with ribavirin and the question is would that be a good thing to do from the Committee and the hypothesis is that you may be able to reduce toxicity in that group. And we've heard what the sponsor things of that and I'd like to hear what the Committee thinks of that.

Dr. Hoofnagle?

DR. HOOFNAGLE: Well, I think you need to ask which disease are treating genotype 2,3 or genotype 1 and genotype 2,3 I think maybe it would be worthwhile to do and I've actually proposed that.

But in genotype 1 you're dealing with a tough disease. I'm not sure that you could design a trial large enough to show a difference between 135 and 180. We're dealing with a biologic here. It's not the typical type of drug. The difference between 180 and 135 is going to be pretty hard to measure, even an intermediate endpoint.

Some of these questions could be answered in retreatment trials and indeed in the HALTC trial. There is some data about ribavirin dosing. Again, you have to know what disease you're dealing with, genotype 1 or genotype 2,3. It's clearly that the dosing of ribavirin and interferon might be quite different.

DR. GULICK: Dr. Sjogren?

DR. SJOGREN: Yes, thank you. Now that I have been pointed out appendix 1, I have been able to digest this a little bit looking at weights and indeed a very nice table of U.S. and non-U.S. people by weights and I think the question of 180 micrograms or 135 micrograms is complex and it cannot be disassociated from the weight of the patients, because if you look at this table and you think okay my fellow American is about 85 kilos, then I'm looking at a sustained response rate of 33 percent overall and I think that just doesn't work. And so I'm thinking now do we need to do a -- I say we, it's a general we, us, the community, do we need to look at this problem as do we need to give interferon on a weight basis such

as is given for the other pegylated interferon? And so indeed, do we need to go back to 90 or 135 micrograms and give it twice a week as some presentation of the ASLD pointed out for other interferons? It is a very complicated question and I think we need help from Roche to tell us, guide us in this respect because obviously, I'm just looking at raw numbers there. They are more privy to the data, but I think that Dr. Hoofnagle is right, if we reduce 180 micrograms for genotype 1 is already starting with 33 percent, we're not going to be able to be winners in this proposition. So if we are going to look at less amount of Pegasys, then we are going to have to look at weight dose or we're going to have look at twice a week or some other variation of that sort.

DR. GULICK: Ms. Thiemann, and then Dr. Englund.

MS. THIEMANN: I feel that part of my purpose here as the community rep is to interject some real life experience into this and as someone who has genotype 1, hepatitis C, as well as HIV, cirrhosis and has not treated yet and who weighs maybe 55 kilograms,

I look at this data and knowing and taking consideration, all the other data that's been presented here and also in other studies on other products, we're also looking at the dose reduction which is almost developing into a strategy and it's certainly a strategy with clinicians who have been treating hepatitis C across the country, dose reduction, modification, in order to get their patients through and try to keep them on treatment over time.

And when I look at this knowing -- and to piggyback on Dr. Hoofnagle's comment about genotype 1, very tough disease. And if you do have the opportunity to dose adjust from that higher dose, get as much drug on board as possible, as much as the patient can tolerate, in that case, and adjust as you go, to me, as a potential patient in a not too distant future, that looks like a strategy to me that I would be willing to accept.

DR. GULICK: Dr. Englund?

DR. ENGLUND: What I would just like to say is that this study was undertaken in good faith

based on the knowledge that was available at the time the study was designed and I think they've done a good job of following recommendations and we have to acknowledge that and today in 2002, is a lot more than what we knew back when the study was designed.

However, I would like them to do a few more analysis of the data that they already have, but I do not think from me personally, I do not want to see another study reinventing everything they've already done. But I would like to see more analysis of what they have and pending that analysis with the FDA input, perhaps do more studies in the future, whether it's redosing or even primary studies directed for, I think, the under represented women as well as the African Americans and other things. So I would like to say that I think we're going down the wrong track. We can't redesign the study that's already completed.

DR. SIEGEL: Let me make entirely clear, we're not asking that one redesign the completed study. Nor are we critiquing the way -- criticizing the way this product was developed. I think good work

went into developing it, but the -- the problem is, of course, we're trying to answer questions as the company is about genotype, viral load, body weight and how it interacts with obesity, gender and other issues and you can only answer so many questions and so it's not a matter of a criticism of the study that there are unanswered questions.

The issue is what are the important ones to focus future research on and that's what we're talking about, not redoing this study, but what are important ones to focus future research on. The analysis, as was pointed out in the FDA bulletin in Appendix 1 does give by weight class response rates, and so there are certainly suggestions of smaller response rates in larger people.

One could ask the question not only -- weight adjusted dosing was not -- our question did not presume that that would be a lower dose. A weight adjusted dosing would likely be a higher dose for large people and a lower dose for small people and it might be more intensive for larger people and so you might want a more intense regimen as a 55 kilogram

person, but the average weight in this disease tends to be rather high, I think in these studies, 85 kilograms and higher in the Schering study and you know, the 100, 110 kilogram people and there's a lot of them in these studies may feel they're not getting as intense a regimen. The toxicities and response rates do seem to vary by weight, although I don't know if we have all the toxicity by weight group here. We do have response rate by weight. But as you see, the numbers get small when you start subdividing into small groups.

DR. GULICK: Thanks for that. We're going to have to bring this to a close. Dr. Fleming?

DR. FLEMING: The study was designed, basically as we all know, looking at the single 180 dose for peg-interferon and that's obviously the most reliable interpretation is what is benefit to risk in that strategy of a fixed dose. If we could readily do so, I would love to know what is the benefit to risk profile with other strategies, with other lower fixed doses, other higher fixed doses, other weight adjusted doses. We can explore these data to try to get some

clues, so we have to be incredibly cautious about those clues. Now if in exploring these data we were looking at efficacy as a function of baseline weight and safety as a function of baseline weight, and we saw a pattern that indicated for lower weight individuals you had greater toxicity, but comparable levels, no change in efficacy, that to me would be a significant clue to suggest that weight adjusted dosing may readily achieve an overall, more favorable benefit to risk profile than the current fixed dosing strategy at this dose, specifically by recognizing that for a lower weight people you could achieve a better benefit to risk with a lower dose. But the data don't suggest that to me. The data suggest to me as I look at this that as you get to lower weights, yes, you do have some evidence of higher safety risks as the FDA showed in their slide 31, but as their slide 22 shows and as Table 17 in appendix 1 indicate that with these lower doses, there seems to be higher efficacy. So it's entirely unclear to me when I look at this whether or not we would do better in benefit to risk at a lower dose or at a weight adjusted dose

or for that matter at a higher dose. Somewhat what this comes down to is as you get increase efficacy, but you have increased safety risks, how do you judge benefit to risk in that setting and do you believe that what you see in these lower dose or these lower weight individuals where you do have substantially higher rates of sustained viral response, but you also have higher toxicity, is that a balance that's acceptable.

So bottom line is I would love to know more if I could know -- if I could, in a readily straight forward way, but looking at these data, it's not clear to me whether the other strategies of lower dose or weight adjusted dose or higher doses as fixed dose would be likely to achieve a different benefit to risk globally than what we got from this specific regimen.

DR. GULICK: Okay, let me try to summarize what we think here. Regarding lower doses of Pegasys, Dr. Fleming summarized nicely saying we need to know more. Regarding the 135 microgram dose, it has appeal on the surface as perhaps providing similar efficacy,

but less toxicity and would be potentially less costly than the 180 microgram dose. However, there's concern about efficacy, particularly in genotype 1.

Dr. Hoofnagle made the suggestion that perhaps for genotypes 2 and 3 or for people who are of lower weight that that dose may be worth investigating further.

Dr. Wong pointed out that a dose modification of 135 brings you down to 90 micrograms which we know is a suboptimal dose, so there's some concerns there.

Regarding weight-based dosing, it certainly makes some sense from the data that we know. Patients are obviously variable in their weights and sizes and appendix 1 is something we focused on that showed a differential response based on weight in the data that we already have.

Dr. Sjogren pointed out other factors may also be important and need to be thought of, including gender and race. However, most people felt this was reasonable to explore for future studies.

Dr. Englund suggested that an analysis of

the present data may actually be -- that we could look further at the relationship between weights and doses with the data that we have.

Dr. Hoofnagle suggested that retreatment studies might be the optimal place to look for future dosing questions.

Let's move to number which talks about the dose of ribavirin. A parallel question, should the sponsor evaluate additional doses of Copegus? If so, please discuss in light of the dose comparison performed in Study 2, what additional doses should be studied?

So let's consider first, should additional doses of ribavirin be studied?

Dr. Fletcher?

DR. FLETCHER: I think the answer to that is going to be yes, but let me make a couple of comments and then I have a question to see if the sponsor has some data.

I think first to just quickly get back to what people have talked about, I think why you would want to look at different doses and weight adjusted

doses is back to this issue of the degree to which weight is correlating or driving response and toxicity and among the variables that we've seen that are important, after you get past genotype, then the only other variable that I've seen so far, you can do anything about is weight. Someone's sex is their sex, their ethnicity is their ethnicity and while it may drive response, you can't change it. On the other hand, weight is a variable that if it's important in drug response, you can alter the dose for weight. So I think there is a fundamental part in terms of why weight is important.

The second point is what confounds this is we're getting combination therapy and so this difference in weight response that we've seen, what's driving it? Is it the interferon component or is it the ribavirin component and I've not seen an analyses and I'm not quite sure I can think of how to do one that would really try to explain that. So we are left with unknown of what's driving this difference in response.

Now my question to the sponsor is in the

case of ribavirin, do you have data on what variability in clearance is explained by body weight?

DR. JORGA: Thank you. We did a pharmacokinetic analysis, as I pointed out on ribavirin and we looked at the effect of body weight on the clearance of ribavirin. Can I have the slide up, please? This is what you're seeing here. This is the body weight range of 55 kilo to 155 kilo and you see a modest increase in clearance with increase in body weight. That's what you see here. It's a relatively modest effect as I pointed out. It's nicely compensated for by the dose adjustment that we are doing with this 75 kilo cut.

Can I have the next slide, please? This was the slide we first presented earlier today already. This is the data from the 800 milligram dose, the orange line. This is what happens if you don't body weight adjust dose which is very tolerated when you see basically a slight decrease in the exposure to ribavirin with increasing body weight. For the patients with genotype 1 which is the more important to keep them in the narrow concentration

range, we think it's inappropriate to do this body weight cut at 75 kilo because we'd like to have them at a certain level in order to avoid under exposure and you also would like to avoid over exposure, by treating them too high. So that's the pharmacokinetic information that we have.

We also looked at the benefit risk in terms of the kilogram for ribavirin dosing and you asked this question earlier, you'd like to see this so that you can really make a judgment and if you allow me go -- to talk you quickly through these data so that you can maybe -- this helps your discussion on this, okay?

DR. GULICK: Sure.

DR. JORGA: Can I slide 6, please? I'm going to focus on genotype 1 patients because these are the critical ones. These are data from our 942 study where we gave Copegus 800 milligrams, 1000, 1200 milligram. You know that for the genotype 1 patients the higher dose was more effective and this is why this is a dose that we've proposed for this population. And you can see here now this body weight

cuts below 65, 65 to 75, 75 to 85 and above 85 and you indeed see here decrease in the response with increasing body weight which is not accounted for by the exposure because of exposure is actually in a quite narrow range.

What you also can see on this slide is that for the lower weight patients below 65, the increase from 800 to 1000 milligram has quite a nice effect on this sustained virologic response. You get a nice increase with it. However, for the heavier patients, there's not much to be gained here when moving from 800 to 1200 milligrams which is a 50 percent increase in dose.

Next slide. I'm just now going to show you briefly anemia as a surrogate for risk, for ribavirin related risk and I'm having here the anemia risk of below 10 grams per deciliter and you can see indeed again the lower weight patients have a higher incidence of anemia which decreases with increasing body weight. It's at both doses, of course, it's more pronounced for the higher dose.

Next slide. As pointed out, this anemia

is usually compensated for by dose modification and it hardly ever causes withdrawal.

Next slide. So this is not just to illustrate this to you in one slide, so that you have a good overview of this. This is a body weight distribution of our patients with a 75 kilo cut. We have in here the 1000 milligram up to 75 kilo and then 1200 milligram above 75 kilo and in order to summarize all these data, I've put up here in green the percentage of same virologic response for these different categories and in the red the risk of anemia for these categories and you can see here that above 65, basically we have a very similar benefit risk when you look at it this way and below 65, there's a different benefit risk as Dr. Fleming actually pointed out that we have a higher response rate, but also a higher risk of anemia.

Next slide. If you contrast this with a lower dose for these lower weight patients, you can see here nicely that you can decrease the risk of anemia by losing this lower dose, but at the cost of quite a substantial decrease in sustained virologic

response and that's the last slide I'm going to show you just to -- to contrast here again, the higher weight people, going from 800 to 1200 doesn't really give a lot of benefit in terms of sustained virologic response and it's questionable by that in even higher dose would actually be more beneficial.

DR. GULICK: Thanks. I think that's a really helpful illustration of these issues.

DR. FLETCHER: Could you put that back up though?

DR. GULICK: We're probably going to put you on the spot a little bit longer, so you might want to stay there.

DR. FLETCHER: This is incredibly helpful data and at least for me I'm a little slow on the uptake so it may take me a little bit to grasp this, but when you go back to just your weight and clearance data for ribavirin and I think your point is right that there's a nice relationship there and from that alone I think I would draw the same conclusion, you would think that the weight adjustment you have made would probably smooth out those differences.

These data, however, tell me that that may not be happening. In other words, that ribavirin pharmacologically may have a much narrower therapeutic window than is accounted for by the weight adjustment that you're doing and so I think it does get back to this question then as to whether a more refined weight adjustment could be used to help them smooth out these differences that you're seeing between virologic response and toxicity.

DR. JORGA: I agree with you. Basically on the kinetic point of view, that's fine. But there remains to be an independent factor of body weight on the efficacy as well as on the toxicity. I think it's up to the clinicians to make a judgment call of what do you want to drive for, for more efficacy for an acceptable safety, that's a clinical call.

DR. GULICK: Just as a practical point of view, can you remind us what dosages the ribavirin tablets come in?

DR. JORGA: Two hundred milligram.

DR. GULICK: Two hundred milligrams?

DR. JORGA: Yes.

DR. SIEGEL: Could you put the slide back up, please?

The clinician doesn't, of course, get to choose how much the patient weighs, although the patient -- it's interesting that you drew the conclusion that -- in the under 65 that the extra Copegus accounts for about the higher anemia rate and the higher response rate and then -- but in heavier patients and I always worry about those patients, being heavier myself, you see lower response rates and lower toxicity rates and you came to the conclusion that you didn't think or know if a more intensive regimen such as giving them the same dose per kilogram that the lighter people got might not bump that response rate up by another 20 percent.

There's no data to -- are there reasons to believe that just larger people are going to be refractory to treatment? You can't treat them as well or is it simply a matter that you're reluctant or don't think it's worth studying whether treating them more intensively would --

DR. JORGA: Of course, this is now looking

plainly at body weight. I mean there's all these other confounding factors. I mean looking at this already, increasing the dose by 50 percent, we didn't see much more benefit. We went even further than this. We went into clinical trial simulations where we developed a model which took all the other things into consideration like cirrhosis and all the other prognostic factors and we were trying to predict what response you would achieve if you give 1600 milligram dose to these heavier people and you could come up with an absolute increase of sustained virologic response of maybe 4 percent, 3, 4, 5 percent which could be substantial for the patients, but on the other hand also from a practical point of view doing such a study is just very difficult.

So we went further than just this analysis. This is just a very simplified way of looking at it.

DR. FLETCHER: Don't sit down yet.

(Laughter.)

Now could also what's going on here is you're just now really seeing two different

pharmacodynamic profiles going on?

DR. JORGA: Uh-huh.

DR. FLETCHER: So let's say at the lower body weight, less than 65, that difference in the ribavirin dose is very important in terms of driving response. Now at the higher body weight, that difference in ribavirin dose doesn't appear to have done anything, but is a difference in overall response now due to the interferon?

So would the higher body weight patient, while perhaps not benefitting from a different ribavirin dose, benefit from a different interferon dose because you just simply have two different pharmacodynamic relationships going on. One has plateau'd and one has not.

DR. JORGA: Do you want to answer that?

DR. HOFFMAN: If can just address that. That would actually be our recommendation and what we're looking at when I showed you that clearance slide over body weight, the information that we had at the far end, we didn't have a lot of patients or actually subjects there. And we think that might be

an area where we can push the dose up for interferon.

We're a little bit reluctant at the other end for the reasons that have been mentioned. These are the patients who respond the best and if we reduce the dose, we may increase the safety, decease the number of dose reductions, but at what cost? So that's the end that we would prefer to go.

DR. GULICK: Dr. Hoofnagle and then we're going to have to move on.

DR. HOOFNAGLE: I think it's very important. We're talking about increasing response rate by four or five percent by adding additional drug expense exposure toxicity so that the 40 percent who would respond at this lower dose were exposed to more unnecessarily and the 50 percent who don't respond at all were exposed.

I think pushing these doses up comes at enormous expense to the people who get away with lesser dose and again this is where retreatment trials are helpful and the resistant patients and then trying these more aggressive regimens rather than exposing everyone to these higher doses of interferon --

DR. SIEGEL: I have to take issue with the premise of that statement. The difference in response rates to this regimen in the first study according to our Table 17 in the heaviest versus lightest patients was 66 versus 36 and then that slide was 66 versus 32 between the heaviest and lightest patient on the more intensive regimen. So we're not talking about 4 or 5 percent. We're talking about 25 or 30 percent differences, if you could achieve the rates in heavy patients that you do in light patients by more intensive regimens.

DR. HOOFNAGLE: You're talking about Asians and you're talking about younger people too. This is very confounded.

DR. GULICK: Dr. Fletcher, the last word.

DR. FLETCHER: The only point I would want to make is that would be right if you treated the whole population with those different fixed doses. I think these data are the ones that make the case that one should look at weight adjusted doses, so your point would be right that if you give everybody higher or give everybody lower, then that risk benefit may

not be worth it, but if you do some individualization of those doses based upon body weight, then that would not necessarily be a case.

DR. HOOFNAGLE: Again, a very small increase in response rate. When you give these drugs for a year --

DR. ENGLUND: That was based on a model. That wasn't based on actual data that she quoted, right?

DR. HOOFNAGLE: Thirty percent of people are having their interferon dose reduced and what, 40 percent of people getting ribavirin dose reduced? Really already pushing toxicity with the regimen.

It's a tough regimen as it is now.

DR. GULICK: Okay, Dr. So.

DR. SO: For those of us caring for these patients, this is not a patient for any drug and increasing higher doses for little yield is really not -- I totally agree with Jay.

Now it's very interesting, if you look at all those under 65 kilos, none of them are U.S. patients. Although I really think for those skinny

Asians who -- they really could benefit from doing a study to reduce the dose and you probably will have more patients who will be willing to participate in treatment because that group of patients, you know, as you can see, maybe genotype plays a role, but their response rate already is like 80 percent and that group might stand to benefit from fine tuning the dose.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I just want to say that he can do the skinny Asians and I want to do us fat Caucasians.

(Laughter.)

DR. GULICK: On that note, let me summarize. Dr. Fletcher started off this question reminding us that both interferon and ribavirin doses may be important and may have different profiles in terms of assessing and balancing safety and efficacy. Also, that weight is probably one of the more important variables because we can actually respond to it as opposed to other demographic factors.

He also noted that the therapeutic index

for ribavirin is relatively small based on the data that we saw.

In terms of additional doses, some differences of opinion on the Committee. I guess an overall consensus that more refined weight adjustment might be of interest. We're constrained by a couple of things. There was concerns about raising doses and increasing toxicity.

Also, the fact that ribavirin comes in 200 milligram pills, so that constrains you in terms of how much refined dosing you can do.

In terms of additional doses, there was some enthusiasm for increasing the doses in heavier patients responding to that very nice curve that we saw. However, people pointed out there are other factors to weigh in. The interferon dose may be more important. We heard about the modeling from the sponsor. Did I say weigh in?

(Laughter.)

Thank you. I'll adjust that. Modeling at 1600 milligrams. We heard from the sponsor of ribavirin did not really produce increases in

activity, at least in the model they used and once again Dr. Hoofnagle reminded us retreatment trials may be the place to explore some of these questions.

Okay, let's move on. Dose and treatment duration. In Study 2, in addition to the two doses of Copegus, two intervals of combination therapy, 24 or 48 weeks were evaluated. Because of an equal randomization, higher risk patients were preferentially placed in the higher dose and longer treatment duration, not possible to compare directly the total SVRs among the four treatment groups. Based on comparisons across randomization strata, genotype 1 achieved higher SVRs with the higher ribavirin dose and the longer duration of therapy. For patients with genotype non-1, neither more Copegus nor a longer duration appeared to improve the SVR. However, this is in a small subset of patients.

There was also concern about genotype 4 suggesting that that particular group might benefit from a higher Copegus dose and a longer duration.

Question 3, if licensed, please discuss what dose of Copegus and what duration of treatment

should be recommended based on viral factors, I presume genotype, that predict treatment response. Are there sufficient data in genotype 2 and 3 regardless of viral load to recommend shorter treatment duration and/or 800 milligrams of ribavirin? And if not, what additional studies should be conducted?

Yes, Dr. Alter?

DR. ALTER: I may be jumping ahead a little bit, but I think I'm a little bothered by the term non-1 genotype. If we don't have sufficient patients in genotypes 4, 5 or 6 to draw conclusions from most of the studies that have been done and in particular, these, then I think we should be limiting our conclusions to genotypes 1 and genotypes 2 and 3 as the -- rather than saying non-1. Because in essence, it only really, the data only addressed genotypes 2 and 3 in the non-1 category.

DR. SIEGEL: That is not what the questions are asking. The non-1 is because -- was in the study design and for the stratification. But the question on the table now is the treatment of 2 and 3

versus 1 and then the next question is about the treatment of genotype 4.

DR. ALTER: I understand that it then says specifically 2 and 3, but I was bringing up the general comment that in many -- in the entire presentation, in general, we would keep referring to non-1 genotypes when in fact the data truly only addressed genotypes 2 and 3. That's all.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: I would say the data are very strong to recommend the shorter duration of therapy and a slightly lower dose of ribavirin for the patients with genotypes 2 or 3 and it's very valuable information.

As far as genotype 4, it's a very diverse, very large genotype. It's a genotype of Africa. You can't kind of do those studies here and look to studies in Egypt and Africa to define that. It may be that strains of genotype 4 seen in this country are different and so I think it's a very heterogenous group and hard to deal with and it is difficult to know what to recommend for patients with genotype 4.

They respond with a rate as high as those with genotypes 2 and 3, but they seem to require the higher doses. And so maybe some fancy viral kinetics might be helpful in this population to see if they're rapid responders or not. But I don't think you'll be able to resolve that very easily and as far as a recommendation, it's a judgment call and a package insert what you would say about this group.

DR. GULICK: What would you propose as long as you brought it up, given the paucity of data?

DR. HOOFNAGLE: The proposed for future studies, you mean?

DR. GULICK: No, proposed for labeling for genotype 4, if anything, just to put you on the spot.

DR. HOOFNAGLE: I think you would recommend a year of therapy.

DR. GULICK: Okay, since we're considering these two questions together, comments on 2,3 and 4 genotypes, other comments, I should say, Dr. Alter?

DR. ALTER: I agree with Dr. Hoofnagle that I think the data are quite strong for the shorter duration, lower dose for genotypes 2 and 3 and the

longer duration, higher dose for genotype 1 and for genotype 4, you know, that's fine. But I think that it has to be clear that the majority of the data really only address genotypes 1, 2 and 3 and that you could do a year's therapy at a higher dose for 4 with the limitations attached to that.

DR. GULICK: Ms. Thiemann?

MS. THIEMANN: Although I understand that the coinfection studies are nowhere near to being completed, there's a growing population of people with HIV hepatitis C coinfection who are being treated in this country for their hepatitis C prior to initiating HIV therapy.

My concern as far as duration of treatment that 12-week cutoff where patients are being discontinued because they don't have the 2 log or greater drop in ACV viral load may not apply in this population and that it's something that really needs to be disseminated out to clinicians across the country who may not have as much experience as some of the people in this room with this population and really should know that they may need to extend that

period before they cut them loose.

DR. GULICK: And we're actually going to get to that in Question 7.

Other thoughts on this?

Yes, Dr. Fleming?

DR. FLEMING: Let me give you a statistical interpretation of these data from the second trial. The trial, by its design, was with a factorial design was really looking at two fundamental questions. One is what is the relative benefit to risk profile of 24 versus 48 weeks of treatment and then also two different doses of the ribavirin. Generally speaking we interpret the aggregate data and the study is powered to interpret what is benefit to risk in the aggregate population.

We are, however, and it's reasonable to do so exploring to try to determine whether or not the optimal choice here in terms of duration in ribovirin dose may be dependent on genotype and titer, higher versus low. Although one has to be very cautious about this. My own sense is what justifies, in fact, concluding effect modification which is what this

whole discussion is about is very strong statistical evidence that there really is a different benefit to risk profile in different subgroups, together with strong biological plausibility for such effect modification, together with hopefully some independent confirmation.

So specifically, as I look at this and we start breaking down this issue of what is the right duration and what is the right of ribavirin, according to the subgroups of genotype 1 versus non-1 which is predominantly 2,3 as well as by high and low titer, there is some considerable evidence that in the nongenotype 1 which is predominantly 2 and 3 that you're not gaining anything in efficacy with the extra time period of therapy, nor with the higher dose.

Conversely, in the genotype 1 high titer, whether you're looking at the 24 versus 48 or the lower versus higher dose of ribavirin, you pick up 20 percent additional sustained virologic response. However, I'm going to separate because in the low titer of genotype 1 it's 10 percent and what I've heard from discussions around the table earlier there

was some considerable biological plausibility that there could be greater effect in what? In the genotype 1 high titer.

So I'm pretty comfortable from what I'm hearing being out on this limb of interpreting a subgroup analysis to say that it doesn't look like you're picking up added efficacy in the 2, 3. It does look like you're picking up added efficacy in the genotype 1 high titer. But in the genotype 1 low titer, I'm really not so sure. There is some evidence of a little bit better effect, but the statistical compellingness of it is less and I haven't heard the strong biological rationale for this and I'd be interested in hearing more about that.

Now the other dimension to this because all of these comments were efficacy is safety and coming back to what I was saying earlier, when we're looking at factors such as genotype 1, high titer, that factor is not only potentially in effect a modifier which is the way we're talking about it now, but it's also a very strong predictor. Those people have much lower response rates.

What I don't know is if that factor is also a predictor for safety. And there's also a bias in the way safety is being reported in 24 versus 48 weeks when you're following the 48 week people longer, so you're not only picking up true enhanced safety risks, but you're picking up more of the unrelated safety. But let me just make the assumption and this is an assumption that safety isn't different in these, across these groups. If that assumption is true, then I come down with the conclusion that it would seem appropriate to recommend the longer duration of therapy in the high titer, genotype 1 and not in the genotype 2,3, but I'm really uncertain about the low viral titer genotype 1 group.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: I think you've made a very important point Tom and if we go back to the old Rebetron, the standard interferon ribavirin data, it showed what you said, that you could get away with a shorter course of therapy in the genotype 1 low level. so the question is why didn't you see this with the peg-interferon?

One thing is that the level that they chose was too high and that's why I ask about the methodology. That's with the problem with recommending to the general physician to use level of virus as a criteria, is that these tests are not yet approved, right? They're not yet approved. They're going to be used somewhat irregularly, so it's hard to say. But I would say that if you had a patient with very low level of virus, let's say 500,000 or 100,000, I'm pretty sure it makes biologic sense that you could get away with six months of therapy.

But so this is the analysis I would ask Roche to do, a little further refinement of titer versus response rate to look at whether there is a cut point where there seems to be equivalence between 6 months and 12 months of treatment.

DR. GULICK: Okay, let me try to summarize this. We considered questions 3 and 4 together. As Dr. Alter cautions us, non-1 genotype does not necessarily mean 2 through 6, but more likely from these studies means 2 and 3. And we all recognize the paucity of data on 4, 5, 6.

General consensus that the data are quite strong for the efficacy of 24 weeks and 800 milligrams of ribavirin for genotypes 2 and 3. Also, that the standard 48 weeks and 1000, 1200 doses are appropriate for genotype 1 and we just concluded the discussion with noting that the results are better in the quote high viral load group, although as pointed out, the low group may not actually be such a low group and that the variability of HCV viral load tests in the community is high.

Also, as Dr. Fleming reminded us, that discussion was really thinking about efficacy rather than safety, although I guess we could assume that 48 weeks is likely to have more toxicity than 24 weeks of the same drugs, just because it's twice as long.

Regarding genotype 4, a few patients studied here, some important differences that may exist. Genotype 4 identified in different places and further studies need to be done.

Dr. Hoofnagle mentioned the Middle East or Egypt as being places to look for that.

In the absence of data, people felt that

the longer course of therapy and the higher dose of ribavirin might be appropriate, although again, there's not much data.

And then Dr. Hoofnagle called for a reassessment of the data to look at the relationship between titer and virologic response based on the studies we've seen to find if there might be a cut off or a logical cut off between high and low titer.

Yes, Dr. Wood?

DR. WOOD: I just wanted to add one point. We have already acknowledged that on a sufficient number of patients to look at genotype 2,3 responses in African Americans, but I think it is important to highlight in the record that that was the one ethnic group in which there was a substantial difference in terms of reducing the treatment duration to 24 weeks in terms of a significantly different sustained virologic response whereas it was comparable in all the other ethnic groups except for the African Americans.

DR. GULICK: Thanks for that final point. Let's move on to Question 5 which is considering

geographic region which we've talked a lot about today. U.S. patients achieved lower SVRs than non-U.S. regardless of the treatment arm. The U.S. patients had a greater preponderance of high risk factors including genotype 1, cirrhosis, older age and higher body weight. In a multivariate analysis, these factors had more of an impact than the geographic region when all was said in done.

Assuming differences across the regions are real, regardless of causative factors, studies conducted predominantly in the U.S. will yield lower SVRs than studies conducted predominantly outside the U.S.

In addition, the overall reported incidents of AEs per patient was higher in U.S. patients compared to non-U.S. patients. Please discuss the implications of these geographical differences and in particular the implications if cross study comparisons are attempted and what additional factors other than the ones mentioned might help explain these differences?

Yes, Dr. Alter?

DR. ALTER: I don't think there are geographical differences of note at this point that could be addressed by this particular study or others. I think that genotype 1, that the genotype is the overwhelming factor and while there may be some differences between U.S. and non-U.S. patients due to cultural or other characteristics, I don't think this is the place to deal with it.

I think it needs really some independent research, whether it's strain or I don't know. We don't tolerate side effects as well as non-U.S. -- I don't know. But I really don't think it has anything specifically to do with this particular drug or regimen.

DR. GULICK: Dr. Sjogren?

DR. SJOGREN: I do respectfully disagree. I think that what the data that we've been presented points very, very -- in a very good manner, that there are differences, geographic differences. I don't know why, but I know that when patients come to clinic in the United States are going to have less sustained viral response and especially when we go to genotype 1

which is 75 percent of our patients and if we just look at the genotype 1 population, two thirds of them are high viral load and one third are low viral load. And so I think, you know, we had asked in the morning and somebody in the afternoon asked to look at the U.S. data and I think we need to look at that in order to make assessments that although regression analysis may point out to genotype 1 as the main factor, still, when our patients come to clinic we know and this is not just for this interferon. It has also been pointed out by the Agency for other interferons that have come along and I think we need to know. We have the data for other interferons. It's out in the open. We need the data for this one so we can make assessments. Maybe it's better, maybe it's not as good, maybe it's the same. And so we need to make some kind of adjustment in our mind to recommend which drug, but without the knowledge is pretty difficult. And I do think that there are differences in the U.S. versus non-U.S. data.

DR. GULICK: Dr. So?

DR. SO: Can I ask a question. I noticed

on the non-U.S. patients, a lot of them are younger, a lot of them are 45 and younger whereas a lot of the U.S. patients are much older. Does that man -- does interferon, this combination therapy is more effective in patients who have a shorter duration of infection versus those who have a much longer duration of infection?

DR. HOOFNAGLE: It has been hard to show a correlation between duration of infection and response. Part of the problem is the difficulty in measuring the duration of infection. We often don't know when it comes on and you'll see a lot of papers about it, but it's a very imprecise measurement.

I think one of the interesting things comparing U.S. and non-U.S. data is the correlation of lack of response with obesity in the U.S. data which doesn't really hold up in the non-U.S. data. It's as if overweight and obesity somehow affect U.S. citizens more with genotype 1 than others. But the confounding factor in here is age. That's very important confounding factor that really may readjust these data entirely.

DR. GULICK: Dr. Weiss?

DR. WEISS: I just wanted to ask though this is not really the subject of this discussion, but in pediatric patients infected with hepatitis C, there is at least the impression that response rates are better, even questions about whether or not you can get by with the monotherapy as opposed to combination therapy and those kinds of things are being actively studied, but I thought that one of the issues was the duration of treatment and of course, that's probably a much bigger differential when you're comparing pediatric duration of treatment than adults and it's probably much smaller degrees when you put all the adults together, but I'm just wondering that is an issue at least with pediatrics in terms with how long they have been infected.

DR. HOOFNAGLE: Yes, most of the data suggests that children respond at a higher rate than adults. A lot of this data suggests that the patient should be treated earlier rather than later, before they get older, before they gain weight, before they get diabetes and hypertension and all these other

complications. That's what the data points to, but it doesn't show it.

Now I guess as Dr. Fletcher pointed out, it would be nice to have a variable that you could change, one of these predictive variables and the one thing you can change is weight so I would propose a study to look at weight loss before starting therapy as something actually that you can do about one of these variables.

DR. GULICK: Dr. Alter, then Dr. Johnson.

DR. ALTER: I just want to point out that I wasn't suggesting that the differences among U.S. patients doesn't need to be evaluated, but rather from the point of view of geography being the factor when this morning the manufacturer showed us multi-varied analysis among genotype 1 patients that geography was not only nonsignificant, but the right end of the axis and in fact, there were other factors including age, gender, body weight, not to mention genotype that were playing a big role. So if we wanted to look at that, then certainly those would be the types of factors that you would want to look at by U.S. versus non-U.S.

making sure that all the categories were the same, assuming that you had any patients and apparently very thin patients don't participate in the U.S. So -- but not the issue of geography itself.

DR. GULICK: Dr. Johnson?

DR. JOHNSON: It has been said women are under represented in this study, both these protocol enrollment groups. I think they're only 30 percent and I still walk away just on a personal note not knowing how to go back to my own clinic in the Deep South with genotype 1, obese and not, black men.

I just can't quite grip on -- I wish that I had seen Roche do these studies in a variety of cities in the United States and maybe we'll get to the same results, but I think there would be a tremendous enthusiasm and I just encourage Roche to maybe generate those kind of studies.

DR. GULICK: Part of the question asks about the validity of cross study comparisons. I guess sometimes it's tempting to put studies from different places together and show graphs next to one another and given some of the issues we've touched

with this question, what's the validity of that kind of data?

Dr. Fleming?

DR. FLEMING: Actually, I had a different set of comments, but let me first respond to your point. Certainly, it's very important to glean whatever insights you can from whatever relevant studies you have about a specific issue, so if we're looking at efficacy of combination therapies here and there are other studies that provide relevant insights to that, meta analyses can certainly strengthen our overall reliability of conclusions about efficacy and safety, especially if we want to start subdividing into subgroups and we want to be able to say something reliable about subgroups.

On the other hand, where it can be very unreliable is if you have one study that shows an odds ratio of 1.23 for experimental therapy against a control and another study shows an odds ratio of 1.4 for another experimental therapy against that same control. You can't put those two sources of information together and say that the second

experimental therapy has been proven to be better than the first. So there certainly are limitations to interpretation what data you're getting across studies.

What I'd like to spent just a couple of comments talking about though is when I read this question I see really two distinct elements. We're talking about a very important covariate here. That covariate is U.S. versus non-U.S.

Any time you're looking at covariate it's important to distinguish whether you're looking at it as a predictor as opposed to an effect modifier. As a predictor, what we're seeing is yes, there seems to be a relationship between US., non-U.S. and overall response rates, 41 percent against 42 against 61 percent, so it does seem that being outside of the U.S. you have a higher response rate.

There are, however, with a multivariate analysis today we're showing is we can explain that at least in part, largely by genotype 1, but also by cirrhosis, older age and weight. Those factors are explaining a good part, but not all of, but a good

part of that difference in having a higher response rate in the non-U.S. patients.

An entirely separate issue is geographic region and effect modifier is the relationship of efficacy on the peg versus Intron A regimen specific to geographic region. That's an entirely different issue. Now this is a subset and boy, you're in treacherous territory when you're looking at subsets because there's a great chance of just -- just as great a chance of being misled as there is to being guided.

Having said that, we do it and we hopefully look at it cautiously and what we see when we look at subsets is you have this 8 percent overall difference, but when you subdivide it by U.S. and non-U.S. it's 11 percent of non-U.S. and 6 percent in U.S. That suggests to me, not proof, that in the U.S. setting the difference in efficacy is less than it is in the non-U.S. but it's certainly suggestive of that and the toxicity, what we're told, that the incidence of adverse events are higher in the population.

So there is, at least, some interesting

suggestion here that in the context of the U.S. population with its distribution of covariates, there may be somewhat lesser of a difference in efficacy between these two combination regimens than there might be outside of the U.S., but again that's a subgroup analysis and this is the kind of thing that I'd love to see validated by other trials before I would really put a lot of credence in it.

DR. GULICK: Okay, let me try to sum up this question. Regarding geographic differences, I think most of us felt it is valuable to consider what happens in the U.S. and to see that data portrayed separately is helpful to clinicians here in the States.

As Dr. Fleming put it is geography really a predictor or an effect modifier here and as a number of people said could geography be explained by the presence of co-factors, notably genotype 1, weight, higher viral load levels, race, age and/or duration of infection.

There could even be biologic plausibility for a difference as Dr. Sjogren mentioned between

continence, strains of the virus perhaps. That's all the discussion of geography and efficacy, but then we also have to consider adverse events. There does seem to be a true difference there for U.S. versus non-U.S. Is this behavioral? Are these other factors that we're simply not measuring, it's simply not clear.

We were warned about cross study comparisons can be valuable for meta analyses, but with high variability sometimes you get limited and unreliable results and that may be the case, given all the variables seen here.

In terms of further studies, people wanted to see more analysis of the cofactors and how they related to geography and validation of this geographic difference in future studies, obviously would be important to look at.

Okay, let's move on. Cirrhosis. Of the three efficacy studies conducted in the Pegasys monotherapy program one specifically targeted patients with cirrhosis. Eighty percent of patients in that study had cirrhosis or bridging fibrosis and about 20 percent enrolled in the two studies we've been

considering today had cirrhosis which is more representative of hep C studies in general. Monotherapy label specifically identifies the cirrhotic population as one in which efficacy has been demonstrated.

In the combination studies, patients with cirrhosis comprise 13 and 25 percent of the patients. Discuss the implications of cirrhosis.

Should clinical development programs for products intended for patients with hep C infection include separate studies for patients with cirrhosis and should patients be stratified with cirrhosis as a variable?

Who would like to start?

(Pause.)

Okay, well, we've answered that one.

Dr. Hoofnagle?

DR. HOOFNAGLE: I think one issue would be in patients with genotypes 2 and 3, you plan to treat them for 24 weeks. What if they have cirrhosis? Is that a reason maybe to extend it to one year? I think the data says no. But in the cirrhotic patients with

genotypes 2 and 3, the response rate is the same. So it is a reason to advise a patient that their response rate is likely to be less, but it does not seem to be a reason to alter the regimen.

DR. GULICK: And the value of selecting that patient population specifically? Should studies be targeted just for patients with cirrhosis as was done in the monotherapy studies?

DR. HOOFNAGLE: Particularly helpful in assessing safety. As we said before one of the big concerns of interferon, especially for a year are severe infections which can be a very big problem for someone with cirrhosis. So assessment of safety -- looking now to these things like using GCSF to maintain white counts, I think that's a group where you would go earlier rather than later to prophylactic antibiotics and so forth. So I think that type of analysis would be good.

Let me say something else about the analyses they've given us. The FDA tried and did, in part, give us the end of treatment versus sustained response and that is -- I like that data because that

tells you the relapse rate.

While in reading these papers the relapse seems somewhat of an arcane issue to you. When you're dealing with a patient, the relapse rate is very important because they've become PCR negative on therapy, so you continued for a year.

What is their chance for a relapse and knowing the relapse weight with each of these therapies, each regimen and cirrhotics and noncirrhotics, genotypes 2 and 3, all those things are very valuable because it gives you a lead about what to do.

Relapse is high with short courses of therapy. If you treat people for two months virtually all relapse. We see the data with six months and with 12 months and the reason why the patients with genotype 1 need 12 months of therapy is the relapse rate. The same proportion become PCR negative because they all become PCR negative by 24 weeks. So what you're doing is decreasing the relapse rate. By giving us that data that give you a hint about future studies of longer courses of therapy and so forth.

Also, I wonder if Roche could provide us with all of these nice slides that you're showing us in follow-up. Those are very helpful.

DR. GULICK: Okay, other comments on cirrhosis?

Dr. Fleming?

DR. FLEMING: Just a brief one that I think the FDA, Table 16, page 18 in their report justifies exactly the comments that Jay was saying at the beginning of his response and that is cirrhosis certainly is, in my words, a predictor. Those people with cirrhosis globally have lower response rates than those without cirrhosis, but it's not, in effect, a modifier as you look at the relative efficacy of these interventions. Basically, whether you have cirrhosis or not, you have the same relationship of the peg having a somewhat higher response rate than Intron A and in turn higher than the monotherapy.

So it seems to be a predictor, but not an effect modifier and as a result it doesn't suggest to me that you would alter the choice of the regimen, at least based on this analysis based on the presence of

absence of cirrhosis.

DR. GULICK: Dr. Wong?

DR. WONG: I guess my comment was really going to be the same as that. I don't know that I would separate out patients with cirrhosis unless it could be shown that presence or absence of cirrhosis is not just, for example, the surrogate for age or duration of infection, things like that. I mean it's going to be difficult to pick that out and are we proposing that separate criteria be made, you know, or separate studies be done for different age groups, separate studies be done for different durations of therapy.

I guess I'm not convinced that the cirrhotic patients are really that different.

DR. GULICK: Dr. Sjogren and then Dr. So.

DR. SJOGREN: In clinic, it is very important to have data. When Ginny Hitcock data came out with the monotherapy of Pegasys was incredibly valuable because 30 percent sustained response monotherapy in cirrhotics was a very good rate and gave us hope that indeed, the combination therapy

would even be better because as we know, cirrhotics don't tolerate the full amount of interferon or ribavirin. So we are left wondering if we apply the concept that we learned from naive patients that don't have cirrhosis to the cirrhotic ones, it just doesn't hold true.

So I think studies for cirrhotics are extremely valuable in clinic because then we will learn much more and we can advise our patients better.

DR. GULICK: Dr. So.

DR. SO: Cirrhotic is very important from a clinical aspect to decide whether to give these patients treatment and what the risk benefit ratio is. You might have shown it before, did any of the patients you treated who had cirrhosis decompensate after treatment?

DR. HOFFMAN: Yes. Decompensation was a very rare event, I think in our whole program of monotherapy and combination therapy. There were a total of two patients with decompensation. And both of those cases I believe were considered to be unrelated to the drug and to the natural history.

DR. SO: Can I just follow up? On all your patients defined as cirrhotic, were they all proven by biopsy or biopsy plus radiologic evidence?

DR. HOFFMAN: Biopsy. There were some rare patients who had ultrasounds because whatever reason they didn't have a biopsy. We're doing that in some of our studies with hemophiliacs and things like that.

DR. GULICK: Is stratification on the basis of cirrhosis desirable at the beginning of a large study like this?

DR. SJOGREN: Either that or a -- like they did with the Ginny Hitcock study, a large study with cirrhotics that will answer the questions. In my concept, it will be either way. I would think that a single study might be easier than stratifying a whole bunch of studies at a later date.

DR. GULICK: Dr. Fleming.

DR. FLEMING: I would say it depends somewhat on the size of the trial and how many other factors you wanted to provide structure for. When I stratify, it's usually because I think it's a

predictor, i.e., the noncirrhotic patients are going to have a much higher response rate than the cirrhotic patients and I want to make sure I don't get confounding and I think it is a predictor, but whether I would stratify depends on whether there are a bunch of other factors that are even stronger predictors or whether my study is going to be large enough that randomization, law of large numbers will kick in.

A separate issue is whether you think its an effect modifier and you can look at that issue whether you've stratified or not. So I think the answer to your question is one that would depend on how many other factors you were going to want to control for and how big your trial was going to be.

DR. GULICK: Okay. Just to briefly summarize here, the data very valuable to consider cirrhotic patients as a separate group in terms of response rate, relapse rate and safety information. So it is valuable, very valuable to see that information and be able to talk to patients about that.

Some suggestions about how to proceed.

Separate studies for cirrhotics is one approach and I think people were pleased to see that with a monotherapy study. However, that may not be necessary. If there are large studies like the ones we saw today, stratification with substudy analysis may be appropriate for that particular group.

Dr. Weiss, number 7 was sort of an optional one.

DR. WEISS: A few people already mentioned it briefly, so maybe we could try to still address that and still get through rest of the questions.

DR. GULICK: Okay. Let's try it. Recommendations for discontinuation of treatment for inadequate early viral response. Ms. Thiemann brought this up before.

In both studies, subjects who did not demonstrate either an early virologic response or an early biochemical response could be withdrawn from the study by 12 weeks and were to be withdrawn if unresponsiveness persisted to 24 weeks. Ninety-six percent of patients who showed no early virologic response by week 12 failed ultimately to achieve an

SVR.

Question 7, please discuss what advised should be provided regarding early discontinuation of treatment for lack of efficacy.

Dr. Wong and then Dr. Sjogren.

DR. WONG: When I first saw this I couldn't tell really what that 96 percent meant. I think it means 96 percent of patients were not, did not have sustained responses whether or not their treatment was continued. Is that correct?

So I think that we really want to -- I would want to know the answer to two questions. One is will they have sustained responses if treatment is continued anyway and will they have sustained responses if it's not. And I guess I'm not sure what that 96 percent means.

DR. HOFFMAN: Hoffman from the sponsor. Slide up, please. Let me answer both the questions first just to explain what this is.

So you determine here whether or not patients meet the criteria for an early virologic response. These are the ones who don't. Of the ones

who don't 96 percent don't have a sustained virological response. Put it the other way, if you don't have response by Week 12 or at least a 99 percent drop, only 4 percent of those patients go on for stayed response.

DR. GULICK: But how many of the 98 continued with their planned treatment?

DR. HOFFMAN: We allow patients to go through Week 24 at which time we gave them their PCR and they were free to leave the trial at that time if they still hadn't responded. There were some patients such was mentioned previously who normalized their ALT and continued in the trial. Not one of them had a sustained virological response.

DR. WONG: But how were there of those?

DR. HOFFMAN: I'm trying to think. It's somewhere around 20, 25 patients.

DR. GULICK: Dr. Sjogren?

DR. SJOGREN: I think I asked this question in the morning if the study was powered to answer this question because I knew you were going to come to us with question 7 and the answer was no.

There is really a look at the data and really interesting look at the data, but when you're in clinic and when you are looking at patients and you are going to tell them that a 2 log drop or a negative -- or a positive RNA is going to make or break their treatment, I don't think we are on solid ground to say that. And unfortunately, there are people out there going on the stump saying just give 12 weeks of pegylated interferon and ribavirin and then if they don't have a 2 log drop or a negative RNA discontinue. I think that may be a disservice without proper knowledge.

I will caution about that. I wouldn't want to see that in the package insert and I would even appeal to Roche to help us out with the education of the physicians that go give talks or the science people that that is not a proper way to go because we are not on solid ground. If they prove it beyond reasonable doubt, let it be, but I think at this point it's not -- should not be used.

DR. GULICK: Dr. Hoofnagle? Drs. Fleming and Johnson.

DR. HOOFNAGLE: This is what we call an early stopping rule. Can you stop early because therapy is futile? Ideally, you would have a market that had a 100 percent negative predictive value. That would be ideal. What the sponsors told us, it's not ideal. They have 96. It's close. If you remember a post hoc analysis of the peg Intron data gave a very similar negative predictive value, I think 97 percent to the same criteria.

So it's not perfect, but it's quite valuable in someone who is not responding at all. Again, it relies upon an unlicensed test and that the physician knows what they're doing, gets the test right when they start therapy and right at 12 weeks to apply this. It also as pointed out applies only to naive patients who are not HIV positive. So it's not universal. I think you have to put a lot of caution to this, but on the other hand, I think you should publicize this data, that this is what it shows, one way or the other.

I think a nice analysis for Roche to do and perhaps Schering is to drag out those three or

four patients that you know were not predicted by this and give data on them. Do they fall by 1.9 logs or had their dosing been interrupted for a while? All those types of things might account for why this occasionally fails.

DR. SIEGEL: As a point of clarification in comparing the data, I believe the Schering data you're referring to were data where viral response was measured at 24 weeks and patients were continued on a year of therapy.

Here, we're looking at viral response measured at 12 weeks and we're noting that they didn't response by 24 weeks, but it's only in a very small subset who actually continued for a year as was pointed out by one of the earlier questions.

DR. GULICK: Dr. Fleming and then Dr. Johnson?

DR. FLEMING: I think Dr. Wong's question is exactly on target because what I understand what we're really being asked here is can we get an early marker as Jay has pointed out that would give us a good sense of whether we have to continue therapy.

The answer to that should be based only on those people that based on that early marker did, in fact, still continue therapy and in fact, when they did still continue therapy, if they didn't achieve benefit, then that would be the nature of the evidence to indicate that with this marker, if you don't have at 12 weeks a virologic response and in spite of continued therapy and I can't tell how many of those 90 odd people still had continued therapy. Those are the only ones relevant to the answer of this question.

My ideal answer to this question would be characterize people at 12 weeks as nonresponders and then randomize that cohort to continue therapy versus not and then look at the outcome. That tells you the reliable answer about whether continuation from that new time zero gives you any net subsequent benefit.

DR. GULICK: Dr. Johnson?

DR. JOHNSON: I feel strongly this should go in the package insert and I thought these were beautiful data and I'm a virologist and the test will get approved and I would want to know that while we're gathering all these data and just as an HIV virologist

and Trip can answer this too, I wouldn't go into treatment if I had no response in an HIV patient at 4 weeks or 12 weeks and keep going. I'd kind of want to stop if something was futile and I think it's important to include these. I think clinicians are smart. They know how to draw their tests. They'll be able to read this and understand this and we'll gather more data, but I would like to see this written in.

DR. GULICK: Dr. Kumar?

DR. KUMAR: I'd like to include that because this is not a benign drug. Neither are the two components are benign. In fact, there's toxicity and cost associated with that. So I think as clinicians, having that information that at the end of 12 weeks if you don't dislog the client, it leads you to a predictive response is there, will give us tremendous help in saying do we want to continue or not.

DR. SIEGEL: Just a couple of comments. There was an earlier comment on this particular question regarding coinfected patients that I'd like to generalize which is that we don't know which of

these data are or are not extrapolatable to coinfective patients and it's just something worth thinking about, but there are so many covariates, that's one that hasn't looked at so we wont' address it.

The other issue is I guess in hearing this discussion, what I'd say is of course what we did in the Schering label as many of you know is put that information in, not to tell people to stop or not to stop, just here's the predictive value and you can decide what to do, but I think the information here on the 12-week data really we have better information as to whether to say that it looks 96 out of 100 who didn't have a virologic response at 12 weeks either would not have a virologic response at 24 weeks and would therefore discontinue or would, but wouldn't get an SVR, but I think at some point we don't know what would have happened to those people if they had continued for 48 weeks as the study was planned because they were stopped and so we'll try to be as descriptive as we can in the label to give the right guidance. But it's not the -- the idea way is I think

was it Tom or a couple of people, I think would be to continue and find out what the responses are contingent on that and that wasn't done entirely here.

DR. WONG: I think just giving the 96 percent, just saying outright you have a 96 percent chance of failure is really overstating what's known.

DR. GULICK: The last couple of -- oh, something important to add?

DR. ALTER: Only that I think it's going to become more and more difficult to evaluate these types or make these analyses because the trials that are going to be planned in the future, many times base how they're going to manage the patients on previous trials. And the high rate of nonresponse in patients who fail to respond by 12 weeks was an originally finding in the original interferon, standard interferon ribavirin trial, if I remember correctly. And I think that was one of the first publications to show 12 week versus evaluating at 24 and so this is going to become more difficult. So either we decide not to build on that previous information with new compounds or we're not going to have the information

just like you're doubting the problem, whether or not the data are strong enough now. It's going to be just an increasing problem.

DR. GULICK: Okay. Dr. Sjogren?

DR. SJOGREN: In the Rebetron trial, as I remember, if you were to stop at 12 weeks, you would have lost 15 percent of patients and so when we were educated on Rebetron we learned that we needed to go to 24 weeks or else we would call it off too soon. And that is my concern.

I don't think I've seen enough to say I should stop at week 12. Besides there is so much variability with the RNAs. It's not easy for a gastroenterologist to realize what a 2 log drop is. And I don't think only gastroenterologists get patients. There are some other specialties that treat patients out there and when you have so many variabilities, so many assays, it's hard to put this on clinicians.

If Roche would come and say negative RNA, then I think we will have a little more maybe -- but 2 log drop or RNA or you know as the FDA pointed out

here, biochemical response, it's a lot of variables that will have to be outlined and package inserts tend to be kind of long and tedious and so I am worried about what is the message that we're going to put out there.

Dr. Alter is saying yeah, the next iteration of interferons may base -- it becomes gospel. I'm very concerned about that.

DR. GULICK: Okay, let me summarize here. Regarding the data about stopping treatment at Week 12 for futility, most of thought this is interesting and important and would be very valuable data to help share with patients particularly with toxicities of the drug. However, some differences of opinion on how strong this data is and how much data -- how we can make decisions based on the data we have or whether we really need some more data.

Lots of devil is in the detail in terms of variability of the tests, the fact that it's unlicensed needs to be performed correctly. Some skepticism about how complicated this might be for clinicians although differences of opinion on whether

clinicians could really handle this and then the point made that none of this applies to the HIV coinfected patient.

Dr. Hoofnagle reminded us that a partial response may still be important, less than 2 logs and Dr. Alter and others echoed that this could have implications for future studies if this is accepted as is right now. We may never be able to perform further studies to look at it.

Most of all, we were reminded that it was people who had no response at Week 12 who actually continued the therapy that could have answered this question and we didn't really clearly see that data today.

Okay, adverse events. Compared to interferon combination therapy, peg-interferon combination therapy was associated with a higher incidence of SAEs, 12 versus 9 percent, including serious infections, a higher incidence of grade 4 neutropenia, grade 3 thrombocytopenia. There is a suggestion that some patients had a blunted ability to respond to infection. Pegasys combination therapy

resulted in a high incident of reversible lymphopenia. Interferon, in general, appears to result in higher triglyceride levels, although again these are nonfasting and not rigorously assessed.

Question 8. Please discuss how best to further evaluate, characterize, and minimize the toxicity of Pegasys and Copegus, specifically with regard to hematologic and infectious events. Note that some of these assessments could be incorporated into the design of ongoing studies such as pediatrics or HIV coinfected conducted in other clinical settings.

Dr. Wood?

DR. WOOD: It would be helpful is someone from the FDA could clarify. Were all those comparisons statistically significant for each of those categories?

DR. SIEGEL: I would say that we don't have any standard for the determination of what statistical significance when you're measuring a large number of adverse events. Are you asking if the p values are less than .05?

DR. WOOD: Yes, between the two groups.

DR. SIEGEL: Because I'm not sure how to correlate those with any -- whether they're statistically significant or not.

I don't know the answer to that question.

DR. GULICK: Dr. Weiss?

DR. WEISS: Well, just maybe to try to kind of simplify some of the issues. I just heard GCSF came up a lot. There's also, I think, some interest perhaps in the erythropoietin with respect to the anemia and I guess those were some of the thoughts that we had are there, thoughts that the Committee would have about maybe how studies can be done to evaluate some of these types of known adverse effects.

DR. GULICK: Can we ask the sponsor? You sort of alluded to the fact that growth factors were now being more routinely written into studies that were going on? Guidance as to how to use them, etcetera?

DR. HOFFMAN: Well, specifically for the coinfection trial.

DR. GULICK: For HIV/hepC?

DR. HOFFMAN: Right. That's the one, that's the group where we put them in.

They may be used freely in there. I mean we let the clinicians use their judgment where before we didn't dress it and they didn't use it unless there's a rare case.

DR. GULICK: Dr. Wong?

DR. WONG: I guess of these adverse reactions, I was less concerned with neutropenia and thrombocytopenia than the serious infections because people's blood counts can be monitored and as they start to drift down one can decide well, I'll adjust the dose of the interferon or I'll adjust the dose of the ribavirin or I'll administer growth factors, but the serious infections come up sporadically without warning and I guess we heard one example in which it was fatal.

And I would recommend that some sort of kind of prospective monitoring system be put into place if this drug is licensed to actually keep track of this in order to see whether the incidence of these unexpected and unpredictable events is really going to

be quite high and I'm afraid it might be.

DR. GULICK: And can I add to that that not having the ANC data for when the patient had the serious infection I thought was very limiting, to be able to judge whether the drug was really causal for the neutropenia which led to the serious infection.

DR. WONG: Even more than that, I think that interferon has -- is clearly known to have immunomodulatory effects other than just mediated through neutropenia. So I think a real formal post-marketing monitoring system for keeping, for tracking these things is -- should be required.

DR. HOOFNAGLE: It's important to point out and it wasn't mentioned in the presentations, that there were exclusion criteria for initial white counts and neutropenia and patients with cirrhosis are likely to have neutropenia. They were excluded from these trials. So when the drug becomes generally available, physicians are going to forget that oh, this was an exclusion criteria that was used.

And so I think this should be kind of underlined, that neutropenia and infections might be a

problem.

I think the analysis also should show whether neutropenia was more common in those patients who developed infection than those who don't. I got the feeling from your average ANC that those who developed infections had pretty average decreases in their ANCs.

DR. GULICK: Dr. Englund?

DR. ENGLUND: I agree. If the company can do a post-registry pregnancy surveillance, then I think we could be doing a post-registry licensing infection surveillance.

I'm concerned. We've seen the bacterial infections. I can't find the slide here. I saw six cases of documented influenza. I'm not so sure it's just bacterial side effects with interferon. I'm concerned about influenza and perhaps some other infections. So I think we need to get the data and it needs to be actively done as opposed to waiting for a few dead people. I think it needs to be some kind of post-marking active surveillance which we have through the FDA have done in other instances and has been done

well in other compounds.

I just want to say we have the example with other biologicals where we're seeing this effect later on and we're finding severe viral infections with some of the other biological response modifiers.

DR. SIEGEL: When you're talking about things like flu though I'm not sure how in an uncontrolled population -- I mean we might learn of associations with neutropenia or with other effects, but we wouldn't really learn about incidents.

DR. ENGLUND: If they die, I think you will.

DR. GULICK: Dr. Sjogren?

DR. SJOGREN: Yes, when I see a grade 4 neutropenia, I get scared and I think it's a cultural thing because we gastroenterologists, hepatologists are not used to seeing that, you know. That's not in the real of our practice. Infectious disease guys, hemon guys see it all the time and so they know what to do better than we do.

So to me, 5 percent grade 4 neutropenia is a concern. At the same time I want to be careful that

we don't give the message that giving growth factors is the way to go. I think those modifications is very good and vigilance of our patients.

As you know, growth factors are very expensive, every injection is $1,000 or more and it also has a slew of side effects that are very well taken for hemon patients in which they're going to die if you don't do something for them because they have lethal diseases. We're talking about hepatitis C, so I think we should not be cavalier in thinking of growth factors, especially when there's no study of this that I know of that has shown that it increases SVRs.

I know it makes people feel good, but at the end of the day we want to see if people get more sustained viral response with those maneuvers for the side effects and for the money than we are asking them to commit.

DR. GULICK: Dr. Hoofnagle?

DR. HOOFNAGLE: Well, we have a paper in this month's Hepatology pointing that about 20 percent of African Americans have constitutional neutropenia

and ANC counts of less than 1500. We've actually treated such patients and they as opposed to patients with cirrhosis usually have no decease in their neutrophils during interferon therapy.

So I think another issue to point out and to start GCSF in such patients would have been a big mistake, I think.

DR. GULICK: Dr. So?

DR. SO: Are we going to actually in the package insert recommend below a certain platelet count, below a certain ANC, might not be suitable for initiating treatment?

DR. SIEGEL: I think following on precedent you won't find statements in the indications or contraindication section. You might well find them in the clinical study section describing the study.

That's the way we usually deal with that --

DR. WEISS: And in the case modifications too, oftentimes in terms of giving parameters for how to dose suggest.

DR. SO: From the clinical standpoint you

deal with these patients with early cirrhosis, low platelet count and for the clinicians, they always say well, if the platelet counts are already 40,000 or 30000 is this a suitable candidate to start this treatment? I mean those are very practical questions.

Clearly, when they have decompensated BNC they are not suitable, right for a candidate, because they were not in this trial and probably people who are not being treated even though they have depression.

DR. SIEGEL: From a practical point of view those are very important questions for the clinician. As we write the labels, we try not to be so tightly adherent to a mission criteria because with careful monitoring and good judgment, sometimes one can treat patients who are outside of an entry criteria and you sort of preclude that from a reimbursement point of view and if you write very narrow criteria. So our tendency for issues such as this, except where we have, well, you know you're talking pretty profound platelet levels and I'm not going to address that specifically, but except where

we have specific major concerns that the data are likely not to extrapolate well as to put in appropriate cautions, warnings where appropriate regarding the risks of thrombocytopenia or adverse events and information in the clinical study section but not unless there's a very strong belief that certain patients shouldn't be treated, exclusions from treatment.

DR. SO: Can I ask Jay from your clinical sense, do you have some cut offs? I mean for the practicing clinician? I mean because that's what they rely on, really.

DR. HOOFNAGLE: Well, the trouble with the platelet count is there's not much one can do about it. With a low ANC count one can use GCSF. With low hematocrit one can use EPO so it's hard to make something like that. I believe the usual cut off for platelet count is about 60,000.

In HALTC, what is the cut off or platelet count? 40? 40. To start? 60 to start. Okay.

DR. SO: See, they have criteria they use so why can't we have some guideline.

DR. MARZELLA: The trial had criteria, but since we did not have a lot of correlation between infections and white counts, particularly when the patient had serious infections we have some concern as to what the appropriate level is.

DR. SIEGEL: I have no problems with the guideline. I think we're just talking past each other in this regard. They probably have entry criteria for a whole bunch of other things too like age and creatinine and other issues. We just don't usually write those into indication statements. If we have a major concern that if someone falls outside that criteria simply shouldn't be treated until we have more information we'll write it. Otherwise, if we have lesser concerns we'll write warnings. Otherwise we'll just write descriptive information. That's all I'm saying. I think in many cases, you know, if somebody falls outside a range that has been well studied, there's reasonable basis for clinical judgment as to whether or not one can or should treat and labels is probably not the best place to deal with that because it's not data driven. It's judgment

driven, but de facto, if you narrow an indication or write a contraindication you do remove the possibility of that judgment at least where if third party reimbursement becomes an issue because it becomes impossible.

DR. GULICK: So treatment guidelines form expert panels may be a better place to address that, based on expert opinion.

Let me try to sum up what we've said about AEs, just --

DR. FLEMING: I'd like to maybe just add one more thought to the answer to question 8 which I'm going to interpret basically in part to be saying how best to further evaluate toxicity of this combination using the very data we have and my sense is the summary, this lead in paragraph here, I'm comfortable with this interpretation of the relative safety of the peg-interferon ribavirin against Rebetron comparison. My concern more is with the need for further interpretation of the safety data from the second trial and under that second trial I'm certainly persuaded that the 12 month versus 6 month is going to

have a higher safety risk and the ribavirin dose is going to have a higher safety risk than the lower ribavirin dose. But I think it's very important for us to get as clear a sense as possible about what is the differential increased risk in safety and what we've said up to this point is for the non-genotype 1 where there's no apparent increase with longer dosing or higher dosing in terms of sustained virologic response, there's not a lot of motivation to engage in those regimens, whereas with the high titer genotype 1 with a 20 percent improvement, there is a strong motivation, but then there's the lower viral titer genotype 1 where the -- what we're getting from efficacy is less. So I think understanding the level of increased safety is really critically important and here's my concern.

In the cohort of people that are on 48 weeks, half of them are from the high titer genotype 1 category, whereas the 24 week only 20 percent are. Is that a confounder? It's clearly a confounder for efficacy. Is that a confounder for safety?

Furthermore, we have longer follow-up of

the 48 week regimen than the 24 week regimen, so we're not only fully capturing related events, we're capturing a larger fraction of the unrelated events in the 48 arm than the 20 -- of the 48 week arm than the 24 week arm.

So subsequent analyses of these safety data I think will be important to get a better sense of what is the true level of increased risk associated with the 48 versus 24 week and the higher ribavirin dose versus the lower so that in these settings such as genotype 1 low titers where the efficacy is more equivocal, we can make a more informed judgment about whether benefit to risk is optimized by longer dosing versus short dosing and higher dose versus lower dose.

DR. GULICK: Okay, just briefly, adverse events. There was a difference of opinion about our enthusiasm for growth factors versus dose modifications. Interestingly, separated along specialty lines. Hepatologists were more concerned about using growth factors and the ID folks were more comfortable with it, for what that's worth.

There was some suggestions about post

marketing surveillance that we would like to see hematologic events, particularly because there were exclusions for low baseline values coming into the study. Serious infections including viral bacterial and fungal called for perspective monitoring of both of these events as time goes forward and post marketing.

It was recognized that the pregnancy surveillance is a very valuable thing and it was a good thing to have here and then Dr. Fleming in his last comment called for subsequent analysis to really try to work through what the risk benefit is of the AEs at the different doses that are looked at.

Okay. Our last question is the approval question and we're going to take a formal vote on it.

Do people feel that we need more discussion time or have we had enough discussion on this? Are we ready to vote? Oh, I see we're ready to vote.

Okay, so I'm going to ask each person in turn to answer this question. No. 9, do these data demonstrate the safety and efficacy of Pegasys/Copegus

for the treatment of patients with chronic hepatitis C infection? So a yes or no vote.

And we'll start with Dr. Sjogren, voting members get to cast votes here.

DR. SJOGREN: My vote is yes.

DR. GULICK: Dr. So?

DR. SO: I vote yes for all because I have to catch a plane.

(Laughter.)

DR. GULICK: You can just vote yes.

DR. SO: Yes, okay.

DR. GULICK: Dr. Alter?

DR. ALTER: Yes.

DR. GULICK: Dr. Johnson?

DR. JOHNSON: Yes.

DR. GULICK: Dr. Englund?

DR. ENGLUND: Yes.

DR. GULICK: Dr. Fletcher?

DR. FLETCHER: Yes.

DR. GULICK: Dr. Wood?

DR. WOOD: Yes.

DR. GULICK: Dr. Wong?

DR. WONG: Yes.

DR. GULICK: Dr. Kumar?

DR. KUMAR: Yes.

DR. GULICK: Dr. Fleming?

DR. FLEMING: Yes, but I'd like to add a couple of sentences.

(Laughter.)

DR. GULICK: I'm not sure that's allowed. Before you add, let me ask Dr. Stanley, are you still with us?

We're voting Sharilyn.

DR. STANLEY: Yes, I know. I voted a resounding yes.

DR. GULICK: Thank you. And the Chair also votes yes.

That makes it 11 votes for yes and no votes for no. And Dr. Fleming wanted to add a couple of things?

DR. FLEMING: Well, I jus would like to clarify at least in my own view what I mean. I'm taking this question safety and efficacy literally and what I see we've clearly established is sustained

virologic response which in general I would consider a marker which means it's clearly establishing biologic activity.

I've been persuaded though as discussed by a number of people, Jay Hoofnagle, Jay Siegel and others that what we're talking about here is not simply 24 weeks post therapy of sustained virologic response but that there is substantial evidence and this is in my words, I don't know if I'm saying something you wouldn't accept, that in a lot of these folks this is eradication and if, in fact, it's eradication then that conveys to me far more evidence of likelihood of benefit.

My worry is we're measuring something at six months and we're trying to project its effect on something 20 to 40 years later. And generally, that's an extremely difficult extrapolation, but if there is substantial evidence out there that says that if you, in fact, have a sustained nondetectable level for six months, that that may readily be in large fractions of people eradication and that's an entirely different matter. That really does provide a strong

plausibility of actual efficacy.

The last point that I'd make though is when we look at benefit to risk, I'm interpreting this literally that you're asking is there benefit to risk, not whether these data establish superior benefit to risk for peg-interferon ribavirin versus Rebetron. I think that's a much harder question to answer. I think there is evidence for efficacy and safety. It's a much more difficult question to answer whether there is superior benefit to risk for these two combination regimens.

DR. GULICK: And I don't think we want to address that question. And let me restate the vote because I want to make sure I said it right. Eleven votes yes, and zero votes no.

With that I would like to thank the sponsor, the members of the panel, the Agency, for their presentations today and the audience for hanging in there.

Dr. Weiss or Dr. Siegel, any final words?

DR. WEISS: Just to thank everybody very much for their comments and their help.

DR. GULICK: And we will close the meeting. Thanks.

(Whereupon, at 4:15 p.m., the meeting was concluded.)