FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ANTIVIRAL DRUGS ADVISORY COMMITTEE (ADVAC)

Wednesday, April 27, 2011

8:00 a.m. to 4:45 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order and Introductions

DR. CARGILL: Good morning. I would like to remind everyone present to please silence your cell phones, your Blackberry, any other devices, if you have not already done so.

I would also like to identify the FDA press contact, Ms. Erica Jefferson, and I think I saw her. If you are present, please stand.

There she is. Thank you. Good morning.

Good morning. My name is Dr. Victoria Cargill. I am the acting chair of the Antiviral Drugs Advisory Committee. I will now call the meeting of the Antiviral Drugs Advisory Committee to order.

We will go around the room and please introduce yourself. We will start with the FDA and Dr. Edward Cox, to my left, and go around the table.

DR. COX: Good morning. Ed Cox, Director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debra Birnkrant, Director, Division of Antiviral Products, FDA.

DR. MURRAY: Jeff Murray, Deputy, Division of Antiviral Products, FDA.

DR. SINGER: Mary Singer, Medical Team Leader, Division of Antiviral Products.

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MS. VALBH: Pritybala Valbh, clinical pharmacist, PharmaKa Consulting.

DR. CONNICK: Liz Connick, Infectious

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DR. KORMAN: Louie Korman, Gastroenterologist, Hepatologist, Metropolitan Gastroenterology Group, Washington, DC.

DR. KNODELL: Robert Knodell, Baltimore VA, Gastroenterology Division, University of Maryland.

DR. CAMARDO: I'm Joe Camardo, head of Medical Affairs at Forest Research Institute.

DR. CARGILL: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members

take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussion of the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Conflict of Interest Statement

MR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the Antiviral Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

the committee's compliance with the federal ethics and conflict of interest laws, covered by, but not limited to, those found in 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee

essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of new drug application, NDA 202-258, boceprevir, manufactured by Merck, with a proposed indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, two medications approved for treatment of hepatitis C infection, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy. This is a particular matters meeting

during which specific matters related to Merck's boceprevir will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflicts of interest waivers have been issued in connection with this meeting.

We would like to disclose that the consumer representative for the Antiviral Drugs Advisory Committee, Ms. Tracy Swan, is recused from participating in the discussions. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the issues being discussed today.

With respect to the FDA invited industry representative, we would like to disclose that Dr. Joseph Camardo is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Camardo's role at this meeting is to represent industry in general and not any particular company. Dr. Camardo is

employed by Forest Research Institute, a subsidiary of Forest Laboratories, Inc.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

I just want to make a quick housekeeping announcement that the sponsor is making extra handouts, and they will be available -- they'll let me know. Thank you.

DR. CARGILL: We will now proceed with the FDA opening remarks from Dr. Debra Birnkrant. I would like to remind public observers at this meeting that while this meeting is open for public

observation, public attendees may not participate except at the specific request of the panel.

Introduction/Background

DR. BIRNKRANT: Good morning. I would like to welcome everyone to our two-day advisory committee meeting on direct-acting antivirals for the treatment of chronic hepatitis C. This is a very exciting time because many new therapies are being developed for this debilitating disease. Over these two days, you will hear about two new treatments for chronic hepatitis C that are members of the protease inhibitor class and were studied in combination with pegylated interferon and ribavirin.

Why do we need new therapies and new treatment strategies? Because there is a significant disease burden, and current therapy has its limitations. Let's start with the disease burden.

Chronic hepatitis C is a global problem, and it's estimated that up to 180 million are infected worldwide. Chronic hepatitis C is also a domestic

problem and upwards of four million of the U.S. population is chronically infected. Notably, of the 5.6 million veterans in Veterans' Health Administration care in 2008, 2.6 percent had a diagnosis of chronic hepatitis C.

Importantly, the incidence of infection in the United States is decreasing, but, unfortunately, chronic hepatitis C-related complications are increasing, such as cirrhosis and hepatocellular carcinoma, with the aging of the infected population. So we expect more liver-related complications in the next 10 to 20 years. And I'm sure the audience is already familiar with the fact that chronic hepatitis C is the most common reason for liver transplantation.

To set the stage for the next two days, I'd like to introduce you to some definitions, starting with the patient populations and how we described them in the trials.

We have the naive population, who received no prior therapy for hepatitis C; the null responder, who achieved less than a 2 log reduction

in hepatitis C RNA at week 12 of combination therapy with pegylated interferon and ribavirin; partial responders, who had a greater than or equal to 2 log drop in HCV RNA at week 12, but did not achieve HCV RNA undetectable at the end of treatment with the pegylated interferon/ribavirin regimen; and, relapsers, where you have hepatitis C RNA undetectable at the end of treatment, following treatment with the pegylated interferon-based regimen, but HCV RNA becomes detectable within 24 weeks of treatment follow-up.

These definitions are described in our recently published draft guidance for drug development for hepatitis C products, and they are aligned with professional societies' guidance, as well.

Let's turn to some definitions that you'll be hearing over the next two days. Rapid virologic response, or RVR, is undetectable HCV RNA at week 4. Why is this an important point? RVR is highly predictive of achieving a sustained virologic response.

Extended RVR, or ERVR, undetectable HCV RNA at weeks 4 and 12. What is sustained virologic response or SVR-24? It's a validated endpoint used in clinical trials and in practice. It's defined as an absence of detectable RNA in serum six months after completing therapy. It's the best indicator of successful therapy of chronic hepatitis C, whose goals are to have fewer liver-related complications, less progression to hepatocellular carcinoma, and fewer deaths.

What's standard of care? Currently, the standard of care for treatment of chronic hepatitis C in naive subjects is pegylated interferon with ribavirin. In general, the treatment duration is 48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3. On average, response rates are approximately 50 percent, with a wide range of 20 to 80 percent. A response rate of approximately 50 percent means 50 percent don't respond.

Why is there such a range? It depends on multiple factors, some of which are genotype, IL28B

status, race, gender, viral load, et cetera.

I wanted to remind you at this point, as we begin our discussions for the next two days, that already with the approved regimens, there are significant toxicities seen.

What is response-guided therapy? It's a treatment algorithm, individualizing treatment based on neurologic response. Why is it important? Because the goals are to shorten therapy, if possible, in those who exhibit favorable viral kinetics and to identify subjects who are unlikely to have a response, thereby limiting side effects and cost.

I'd like to now introduce a concept that you'll be hearing about today and tomorrow that was developed by our pharmacometrician group. It has helped us determined various durations of treatment for different populations.

It's based on a premise that the treatment-naive population already contains subpopulations of each possible PR responder group. Data for how treatment-experienced patients may respond are

within data from treatment-naive patients.

Our pharmacometrician group found that prior non-responders demonstrate similar virologic response at week 4 of initial or subsequent PR treatment. The analyses that we will present support that early virologic response may be more important than previous exposure to pegylated interferon and ribavirin in determining outcomes.

I showed this slide back in 2006 when we had a two-day advisory committee meeting on drug development for hepatitis C products. What was true then is true now. The pipeline is still full, and over these two days, we'll be hearing about the two products who are the first from that pipeline to emerge.

Lastly, I'd like to end with this slide. These are milestones in the therapy of chronic hepatitis C, and I'm sure the majority of you have seen this slide in one format or another because it comes from a compilation of various authors and investigators' data.

What we have here are the approved

medications for treatment of chronic hepatitis C over a timeline from the early '90s to the future. On the Y-axis, we have sustained virologic response. As you can see, in the early '90s, with interferon either 6 months or 12 months, response rates were quite low. As we added ribavirin, the response rates increased to 34 percent, on average. When we added pegylated ribavirin, response rates jumped to approximately 55 percent.

The future does look quite promising and now it's possible that we have drugs that can increase the SVR rates to more than 30 percent above what standard of care yields today.

Before I close, I would like to thank our FDA review teams who worked tirelessly on these complex priority applications. I would also like to thank the companies for developing these new products and conducting the clinical trials. And I would like to thank the patients who enrolled in these studies for their contributions to finding better therapies for the treatment of chronic hepatitis C. Thank you very much.

DR. CARGILL: We will now continue with FDA remarks from Dr. Jeff Murray.

DR. MURRAY: I'm going to continue with some opening remarks focusing on today's topic, which is for consideration of a new hepatitis C virus protease inhibitor called boceprevir, proposed trade name Victrelis, sponsored by Merck & Company.

So this will suffice as some opening remarks on today's topics but also cover the charge to the committee, which usually occurs later in the agenda. When you get to that part, you can just cross it off now, and we'll be ahead.

So I'm going to briefly summarize the agenda and questions, and I want to summarize the committee's role in these proceedings. Then I'm going to offer some remarks about balancing risk and benefit, which is, in essence, the primary mission of this committee today.

I will briefly summarize the clinical benefit of SVR, as Debra kind of already did, and then speak to the need to consider risk-benefit for each of the issues outlined in the committee

questions. I'll then briefly remark on considerations for requesting post-marketing trials and studies.

So after my remarks today -- this is a brief summary of the agenda -- there will be presentations by Merck, time for some clarifying questions, presentations from FDA. We'll have lunch. There's a open public hearing. People have already signed up. It lasts about an hour. Then we'll have more questions from the committee to the presenters, and then the committee will be asked to address the questions that FDA has posed.

A shorthand version of these question, number one, we're going to ask the committee to comment on safety. The second question will be an overall risk-benefit decision and vote yes or no for marketing approval. The third question involves including null responders in the indication. The fourth question is multipart and addresses response-guided therapy, the best duration for various subgroups, including treatment-naive late responders, black patients,

patients with fibrosis/cirrhosis. The last question will be what types of post-marketing studies/trials should be done.

So the Antiviral Drugs Advisory Committee has members and consultants of various backgrounds, and, by and large, our committee members were chosen based on their expertise to address our most common products, which are HIV and hepatitis C drugs currently. So the committee now consists of a union of hepatologists and infectious disease experts, particularly experts with HIV background.

I'm going to say that lessons learned from HIV may be helpful and offer some grounding in decision-making. However, I caution us all not to over-generalize from one virus to another. As an example, let us consider the term, again, "treatment-naive." I bring this example up because this issue will be a recurring theme for both days of this meeting.

When we think of the term "treatment-naive" for HIV and antiretrovirals, we think of a population that is largely homogenous and consists

mostly of patients harboring wild type virus in which the vast majority is expected to respond. But treatment-naive for hepatitis C and interferon and previous interferon treatment is quite different. The majority of HCV naive patients are expected not to respond. And this population has heterogeneity, and this is an important concept. Treatment-naive patients consist of people who are already intrinsically responders, relapsers, partial responders, and null responders, with various degrees of interferon responsiveness.

So after the committee discusses the safety of boceprevir in question 1, they'll be asked to weigh the overall risk-benefit of adding a direct-acting antiviral, in this case, boceprevir, to peginterferon and ribavirin. And you'll have to consider gains in SVR and weigh that against the addition of toxicity to peginterferon and ribavirin.

To help with the benefit side of the equation, I'm providing some background on the use of SVR as a primary endpoint. In short, FDA views

sustained virologic response as not only a virologic measure but also as a clinically validated endpoint, and this is stated in our draft guidance that was released last year.

In a great review by Pearlman and Traub, recently published in Clinical Infectious Diseases, they summarize multiple studies which support this. There have been multiple -- in fact, 19 cohort studies comparing the outcome between SVR and non-responders which showed a variety of favorable outcomes for those who had achieved SVR compared to those who did not, including decreases in decompensated liver disease, decreases in hepatocellular carcinoma, decreases in mortality, and even reductions in things like diabetes and hyperglycemia.

The largest, most recent cohort was the VA cohort in over 16,000 HCV infected patients with high rates of co-morbidities, including smoking and diabetes. All were treated with a peginterferon/ribavirin regimen. Over 7,000 patients had SVR, and, notably, there was a

significant and a substantial reduction in overall mortality with an adjusted hazard ratio of .67 or 33 percent reduction in overall mortality over mean follow-up for four years.

So I think this cohort and others tells us that treatment of hepatitis C and achieving SVR translates into substantial clinical benefit.

When drugs are in development, FDA has to balance information, getting complete information with availability. There is a tradeoff between getting a drug to the market sooner, particularly one for treatment of a serious illness and a tradeoff of having complete information of every patient subgroup or potential drug interaction that one might want to investigate. In fact, some have suggested that the DAAs coming before the committee these two days should have been made available sooner after Phase 2.

We thought a Phase 3 program was necessary, and that's what we're here to discuss today. I think what we've discovered is that a good Phase 3 trial answers a lot of questions, but it also

generates a lot of questions, and I think that's the case here today given the complexity of hepatitis C therapy.

In these Phase 3 trials, we see that there are many baseline and on-treatment factors that play a role in the primary outcome and for selecting the optimal duration of therapy. These include previous response, null, partial relapse, race, presence of cirrhosis, week 4 response, just to name a few, and these factors also have effects on one another.

It's difficult to design a Phase 3 trial from the outset that can address each and every one of these potential factors and its effect on outcome. Sometimes we don't learn the importance of any one of these until we see the results and analyze them from the Phase 3 trials.

So the hardest question proposed to the committee today involves selecting the best duration of treatment for certain important subgroups. To make this risk-benefit decision, the committee will need to balance optimizing SVR while

trying to minimize additional toxicity.

Prospectively defined and statistically powered comparisons are not available for all subgroups of interest. Despite this fact, FDA still needs to make labeling recommendations in the face of a degree of uncertainty and in the setting of incomplete data.

Thus, we are asking the committee to answer difficult benefit-risk decisions based on the totality of evidence, including randomized comparisons and some retrospective analyses. We are asking this question, importantly, with patient interest in mind. Patients need not and should not be exposed to additional toxicity if there is a low likelihood of additional benefit.

Finally, I would like to make a few comments on post-marketing studies in order to give the committee some background parameters on what is generally expected under the regulations. First, some semantics.

The term "trial" is used when asking for investigations that are clinical and prospective,

generally. The term "studies" refers to nonclinical investigations or observational clinical cohorts.

Next, post-marketing investigations can be divided into requirements or commitments. Requirements fall under the following categories: pediatric trials under the Pediatric Research Equity Act; accelerated approval to confirm clinical benefit, which doesn't apply here because we're talking about an endpoint we consider to be validated for that purpose; but probably the most pertinent for today are required studies to address safety issues. These became requirements under the Food, Drug Amendment Act, the FDA Amendment Act of 2007.

Safety investigations that can be required under FDAAA include trials to investigate adverse reactions. Some examples would be signal confirmation and evaluation, frequency of the adverse event severity, risk factors, and management. Safety issues can also be drug-drug interactions, and, also, drug resistance is

considered a safety issue. And investigations can be trials or they can be studies.

Post-marketing commitments, on the other hand, are voluntary agreements from the sponsor and usually include investigations to evaluate new indications, different aspects of efficacy, or exploratory studies based on theoretical hypothesis or long-term follow-up without specific safety concerns in mind.

For both cases, post-marketing trials should be individual investigations that can be conducted in a specified time frame period and have a discreet starting and stopping point. Long-term follow-up investigations without a specified stopping point or analysis point are discouraged. We want these investigations to be delivered in a specified time frame and to be considered for labeling as appropriate.

With these remarks, I will turn the agenda back to the chairperson, and I thank you very much for your attention.

DR. CARGILL: Thank you, Dr. Murray.

We will now proceed with the sponsor presentations. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the

beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now begin the sponsor presentations.

Sponsor Presentation – Laurie MacDonald

DR. MACDONALD: Thank you, Dr. Cargill.

Members of the committee and the FDA, good morning. I'm Dr. Laurie MacDonald, and I'm an infectious diseases physician in the Regulatory Affairs Department at Merck. It's our pleasure to bring you the data on boceprevir for the treatment of chronic hepatitis C infection.

After this brief introduction, Dr. Jan Albrecht will present the clinical efficacy data on boceprevir, and then Dr. Clifford Brass will present the resistance and safety data. And finally, Dr. Keith Gottesdiener will present a summary of the benefit-risk.

There's a substantial unmet medical need for

new therapies to treat chronic hepatitis C infection. Chronic hepatitis C is a major public health issue in the United States. It's estimated that 3.2 million Americans are chronically infected with chronic hepatitis C.

In the U.S., infection with hepatitis C virus genotype 1 is the most common and is also the least responsive to approved therapies. African-Americans and persons with liver cirrhosis have even lower response rates. Hepatitis C is a leading cause of liver cirrhosis and hepatocellular carcinoma and is the leading indication for liver transplantation.

There are limitations to current chronic hepatitis C therapies. The goal of treatment is sustained virologic response, which is defined by undetectable HCV RNA at 24 weeks after the end of treatment. Currently, the recommended treatment for chronic hepatitis C genotype 1 infection is a 48-week course of peginterferon and ribavirin. Treatment is often poorly tolerated because of side effects that may prevent patients from completing a

48-week course of therapy.

Only about 40 percent of patients with genotype 1 infection achieve a sustained virologic response with the current standard of care. The development of orally administered direct-acting antiviral agents is ushering in a new era in the treatment of chronic hepatitis C infection.

The mechanism of action of boceprevir is inhibition of the NS3 protease. Hepatitis C is a single-stranded RNA virus. The genome codes for the synthesis of a single large polyprotein. The HCV NS3 protease is responsible for cleaving the polyprotein into functional viral proteins. Boceprevir is a protease inhibitor of the ketoamide class. It potently inhibits viral replication by binding reversibly to the active site of the HCF NS3 protease.

The safety and efficacy of boceprevir has been evaluated in an extensive Phase 2 and Phase 3 clinical development program, which is briefly summarized on this slide.

RESPOND-1 was an early Phase 2 dose-finding

study, enrolling patients who had previously failed peginterferon and ribavirin treatment. SPRINT-1 was a Phase 2 study enrolling treatment-naive patients and was the first study to randomize patients to proposed clinical dose of 800 milligrams three times a day.

RESPOND-2 and SPRINT-2 are the two pivotal Phase 3 studies that demonstrated the safety and efficacy of boceprevir administered with peginterferon alfa-2b and ribavirin in previous treatment failure patients and in treatment-naive patients.

Additionally, a Phase 3 study has recently been completed confirming the efficacy of boceprevir when administered with peginterferon alfa-2a and ribavirin.

There are several ongoing studies, one enrolling HIV/HCV co-infected patients and one comparing the use of erythropoietin versus ribavirin dose reduction alone for the management of anemia.

Finally, there are two rollover studies, one

providing boceprevir to patients who failed to achieve a sustained virologic response in a peginterferon and ribavirin control arm of a previous boceprevir study and a long-term follow-up study evaluating the durability of response. Our presentation this morning will focus primarily on the results of the two pivotal Phase 3 studies.

In the pivotal Phase 3 studies, boceprevir has been shown to have a favorable benefit-risk profile. Boceprevir produced superior sustained virologic response rates compared to standard of care in both treatment-naive and previous treatment failure patients. A novel response-guided therapy algorithm which individualized treatment duration based on on-treatment HCV RNA responses allowed early responders to receive shorter durations of therapy.

The safety of boceprevir has been evaluated in over 1500 patients who received boceprevir for up to 44 weeks in combination with peginterferon and ribavirin. The safety profile of boceprevir largely reflects the known safety profile of

peginterferon and ribavirin standard of care. Incremental hematological side effects with boceprevir are manageable and are not treatment-limiting.

The proposed indication for boceprevir is for the treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon and ribavirin in adult patients with compensated liver disease who are previously untreated or who have previously failed therapy. Boceprevir is administered at a dosage of 800 milligrams three times a day with food. Treatment duration is individualized using a response-guided therapy algorithm.

Merck has several consultants in attendance today, and I'd like to acknowledge them. We have Dr. Bruce Bacon, Professor of Medicine at the St. Louis University School of Medicine; Dr. Gary Koch, Professor of Biostatistics at the University of North Carolina at Chapel Hill; Dr. Fred Poordad, Associate Professor of Medicine at the David Geffen School of Medicine, UCLA; and, Dr. Jerry Spivak,

Professor of Medicine and Oncology at the Johns Hopkins University School of Medicine.

I will now ask Dr. Jan Albrecht, who has been involved in hepatitis C research for many years, to present a detailed discussion of the efficacy data that support the use of boceprevir for the treatment of patients with chronic hepatitis C infection.

Sponsor Presentation – Jan Albrecht

DR. ALBRECHT: Good morning. On behalf of Merck, I'm pleased to review the efficacy results of the Phase 3 studies supporting the use of boceprevir in combination with peginterferon plus ribavirin for the treatment of chronic hepatitis C in adult patients. During the presentation, for purposes of brevity, peginterferon plus ribavirin will be referred to as peg/ribavirin and capital PR will be used in the slides.

During the past decade, there has been significant progress in successfully treating patients with chronic hepatitis C. Response rates have increased from approximately 10 percent in the

1990s to approximately 40 percent with the current standard of care, peg-interferon plus ribavirin. The addition of boceprevir to peg-interferon plus ribavirin is another significant step forward.

The efficacy review of boceprevir in combination with peg/ribavirin will include a description of the key concepts from the Phase 2 program that supported the design of the Phase 3 studies, a description of the study designs, the key efficacy results from the pivotal studies, and will conclude with recommendations for treatment.

Phase 2 outcomes were used to design the Phase 3 studies. In Phase 2, we evaluated boceprevir in combination with peginterferon plus ribavirin in previously untreated patients, treatment-naive, for treatment durations of 28 and 48 weeks. Both 28 and 48 weeks of treatment were significantly more effective than peg/ribavirin for 48 weeks alone.

Early anti-HCV response was shown to predict treatment duration. Patients who became HCV RNA undetectable by treatment week 8 had a similar

response rate whether they were treated for 28 or 48 weeks of treatment, while patients who responded later required 48 weeks of treatment. This data provided the basis for a treatment strategy of response-guided therapy in which duration of treatment is based on time to undetectable HCV RNA. We also confirmed that 800 milligrams three times a day is on or near the plateau of both the dose exposure curve and the exposure response curve.

The week 4 peg/ribavirin lead-in was shown to provide an assessment of interferon responsiveness and to be an important prognostic factor for SVR. A peg/ribavirin four-week lead-in prior to boceprevir treatment was used for the Phase 3 studies.

Two boceprevir treatment strategies were assessed in the Phase 3 studies. Boceprevir added to the peg/ribavirin 48-week regimen administered as four weeks of peg/ribavirin lead-in and 44 weeks of triple therapy. Response-guided therapy, in which treatment duration is based on time to undetectable HCV RNA; early responders, defined as

those patients having undetectable HCV RNA by treatment week 8 who receive a shorter duration of therapy; late responders, defined as those patients whose HCV RNA first becomes undetectable after week 8.

Two pivotal Phase 3 studies were conducted in patients with chronic hepatitis C and genotype 1, one study in previously untreated patients, treatment-naive, and the other in patients who had previously failed treatment with peginterferon alfa-2a or alfa-2b plus ribavirin treatment failures.

The study in treatment-naive patients, SPRINT-2, was a multicenter, double-blind, randomized Phase 3 study comparing peginterferon alfa-2b plus ribavirin to two boceprevir-containing regimens in combination with peginterferon plus ribavirin. Patients were adult with chronic hepatitis C genotype 1 with compensated liver disease. Peginterferon alfa-2b was administered according to the U.S. label. Ribavirin was given orally using weight-based doses of 600 to

1400 milligrams per day in a divided dose twice daily.

The study included three treatment arms, a peg/ribavirin control and two boceprevir-containing regimens. All patients received peg/ribavirin for four weeks in a lead-in phase. At the end of the lead-in, patients in the boceprevir control arm had a boceprevir placebo added to their regimen and received peg/ribavirin plus boceprevir placebo for an additional 44 weeks.

In a parallel boceprevir-containing arm, patients had boceprevir added to their peg/ribavirin and were treated for an additional 44 weeks. The third arm evaluated a response-guided therapy regimen based on detectability of HCV RNA at treatment week 8. At the end of the lead-in, all patients had boceprevir added to their treatment and received 24 weeks of boceprevir plus peg/ribavirin.

Patients with undetectable HCV RNA at treatment week 8 who remained undetectable through treatment week 24, early responders, completed

treatment at treatment week 28. Patients with detectable HCV RNA at treatment week 8 who became undetectable by treatment week 24, late responders, had their boceprevir replaced by placebo and received an additional 20 weeks of treatment, for a total of 48 weeks of treatment.

Patients in all treatment groups who remained HCV RNA detectable at treatment week 24 were discontinued from treatment, the futility rule for the study. Patients were followed after the end of treatment for 24 weeks, at which time their response to treatment was determined, SCR, HCV RNA undetectable versus non-responder HCV RNA detectable.

SPRINT-2 enrolled two cohorts of patients. Patients in each cohort were randomized equally to the three treatment groups. Non-black and black patients were enrolled separately because of the known lower SVR rates in black patients.

The goal was to assure that adequate numbers of black patients were treated to assess the impact of boceprevir on this important subgroup; 938 non-

black and 159 black patients were enrolled. Of the black patients, 85 percent identified themselves as African-American.

Patients were stratified by baseline HCV RNA level and genotype -- and HCV-1 subtype 1a or 1b. Base line liver histology was assessed by a central pathologist using the METAVIR score. The METAVIR score is a semi-quantitative score that assesses the fibrosis component of liver histology. The fibrosis component of the score goes from zero to 4, no fibrosis to cirrhosis. During the presentation, fibrosis zero, 1, 2 and 3 will also be referred to as no fibrosis and F4 as cirrhosis.

HCV RNA was measured by polymerase chain reaction using the Roche TaqMan version 2 with a lower limit of detection of 9.3 international units per milliliter. Lower limit of detection was used for all decision points during the study and for determination of SVR.

The study's primary efficacy endpoint was sustained virologic response rate, SVR, defined as a patient having an undetectable HCV RNA at

24 weeks post-treatment. The population for the primary endpoint was all randomized patients receiving one dose of any study drug, the full analysis set, or FAS.

The primary comparisons for the study were designed to demonstrate the superiority of each of the boceprevir-containing regimens compared to the peg/ribavirin control. SVR for the boceprevir/peg/ribavirin 48-week treatment group was compared to the peg/ribavirin control. And if that comparison was statistically significant at the alfa-equal-.05 level, then the response-guided therapy group was to be compared to the peg/ribavirin control.

The key secondary endpoint for the study was SVR in patients who received one dose of boceprevir or placebo, the modified intent to treat analysis, mITT. Patients who discontinued treatment during the peg/ribavirin lead-in were excluded from the analysis, allowing a more precise estimate of the effect of boceprevir.

The key demographic and disease

characteristics of the patients included in the study are shown by cohort, non-black versus black. The study was conducted in North America and Europe, and the patient characteristics, in general, are reflective of these regions. Approximately two-thirds of patients were male with a mean age of around 50. Approximately three-quarters of the patients were from North America, mainly the United States.

There were nearly twice as many patients with HCV subtype 1a compared to 1b, reflecting the distribution between the U.S. and Europe. Most patients had high baseline viral loads, approximately 9 percent had advance liver fibrosis, and, overall, the patient characteristics were similar across the three treatment groups.

The disposition of patients was included in the briefing book and so will not be discussed in detail. Patients were randomized and treated in the study with 363 in the peg/ribavirin control, 368 in the boceprevir response guided-therapy arm, and 366 in the boceprevir/peg/ribavirin 48-week

arm.

The primary efficacy outcome for the study is sustained virologic response rate in all patients, blacks and non-blacks combined. Subsequently, the data will be shown for the non-black and black patient cohorts separately, but for most analysis, the results will be presented for the combined population.

On the Y-axis is the percent of patients achieving SVR and on the X-axis the three treatment groups. The peg/ribavirin control is in white, response-guided therapy with boceprevir in yellow, and the boceprevir/peg/ribavirin 48-week regimen in orange. Ninety-five percent confidence intervals are shown for each of the SVR relapse rates. This format will be used for all results in the presentation.

In this overall analysis, the SVR rates are significantly higher in patients receiving a boceprevir-containing regimen compared to peginterferon plus ribavirin, 63 percent in the response-guided therapy arm and 66 percent in the

boceprevir 48-week arm compared with 38 percent in the peg/ribavirin control, with a p-value of less than 0.0001 for each of the boceprevir-containing regimens versus control.

The high SVR rates in patients receiving a boceprevir-containing regimen are achieved through both a higher response rate during therapy and a lower rate of relapse following the end of treatment. Relapses in the boceprevir-containing regimens are approximately one-half of those in the peg/ribavirin control.

The superiority of the boceprevir-containing regimens compared to the peg/ribavirin control, overall and across patient subgroups, is shown in this forest plot. Odds ratios and corresponding 95 percent confidence intervals are shown for response-guided therapy and boceprevir/peg/ribavirin 48 versus the peg/ribavirin control for the overall SVR, as well as for each subgroup. Dots to the right of the vertical line represent a higher SVR for boceprevir versus the left of the vertical line for the

peg/ribavirin control.

As shown, for the two boceprevir treatment regimens, response-guided therapy on the left and boceprevir/peg/ribavirin 48 weeks on the right, the boceprevir regimens have higher SVR rates compared to the peg/ribavirin control in all key subgroups, including race, baseline viral load, gender, age, fibrosis score, HCV 1 subtype, and regions where the studies were conducted. For both the response-guided therapy group and the boceprevir/peg/ribavirin 48-week group, these data demonstrate the strength of the overall treatment effects with boceprevir, as well as the consistency of treatment effect across subgroups.

When the two patient cohorts enrolled in the study are analyzed separately, the SVR rates for each of the two groups, non-black and black, are significantly higher in patients receiving a boceprevir-containing regimen compared to the peg/ribavirin control. On the left side of the slide, the SVR rates in non-black patients are 67 and 68 percent for response-guided therapy and

boceprevir/peg/ribavirin 48-weeks, respectively, compared to 40 percent for the peg/ribavirin control.

Focusing on the response rates in the black patients, SVR rates in black patients, shown on the right, are 42 percent for response-guided therapy and 53 percent for boceprevir/peg/ribavirin 48-week compared with 23 percent for the peg/ribavirin control. For both non-black and black patients, the increase in the SVR for the boceprevir-containing regimens is statistically significant compared to the peg/ribavirin control.

Consistent with historic response data, the overall SVR rates for black patients are lower than in non-black patients receiving the same treatment regimens. However, the advantage of adding boceprevir to peginterferon plus ribavirin in black patients is clearly evident.

The response rate in the black patients is 11 percent lower for boceprevir response-guided therapy compared to the boceprevir/peg/ribavirin 48-week group. In an effort to understand the

difference in these response rates, we conducted additional analysis.

The first analysis is the mITT analysis in which patients who discontinued treatment during the peg/ribavirin lead-in and who never received boceprevir are excluded. The focus for this slide is the SVR rates for black patients, shown on the right. The data for non-black patients are also shown on the left for completeness. The FAS response rates are shown in the body of the response bars, with the mITT response rates on the top. The difference in response rate is represented by the crosshatch

In the mITT analysis, SVRs are 47 percent for response-guided therapy and 53 percent for boceprevir 48 weeks versus 26 percent for the peg/ribavirin control. The 5 percent increase in the response rate in the boceprevir response-guided therapy group is a result of five patients in the response-guided therapy arm discontinuing treatment during lead-in, prior to receiving boceprevir, versus no patients in the boceprevir/peg/ribavirin

48-week arm. This analysis explains about one-half of the difference in SVR between the boceprevir response-guided therapy group and the boceprevir 48-week groups for black patients.

The presence of liver cirrhosis can have an effect on response to treatment. Therefore, we assess the SVR by the presence of no cirrhosis versus cirrhosis. Non-black patients are shown on the left side of the slide and black on the right side.

For each patient group, no cirrhosis, F0 to 3, is shown on the left side and cirrhosis, F4, on the right side. In black patients without cirrhosis, the SVRs are similar for the two boceprevir-containing regimens, 50 percent for response-guided therapy and 54 percent for boceprevir 48 weeks.

In black patients with cirrhosis, F4, the numbers of patients are too small to make an assessment of the response. For non-black patients, the SVRs for both of the fibrosis categories and the treatment groups within the

categories are nearly identical. For black patients without cirrhosis, the recommended treatment duration is response-guided therapy.

The goal of response-guided therapy is to significantly shorten the duration of treatment in patients who rapidly achieve an undetectable HCV RNA. The response-guided therapy regimen was included in the study to confirm that there is a group of patients, early responders, who can be treated for 28 weeks and have a response equal to that of patients receiving boceprevir added to the standard 48-week regimen of peginterferon/ribavirin.

As a reminder of the study design, this slide shows the treatment regimens for early responders in the response-guided therapy and the boceprevir 48-week treatment groups.

In order to compare the efficacy of response-guided therapy for early responders to a like group in the boceprevir/peg/ribavirin 48-week arm, we conducted an analysis in patients in the boceprevir response-guided therapy group who were

early responders, HCV RNA undetectable at treatment week 8 through treatment week 24, and stopped treatment at treatment week 28, the yellow bar on the treatment diagram on this slide, with patients in a parallel boceprevir 48-week group, who were also early responders, orange bar on the treatment diagram on this slide, and continued on treatment for 48 weeks.

When the non-black and black cohorts of patients are combined, overall, 44 percent of patients meet the criteria for early response, treatment week 8 through treatment week 24 undetectable.

In these early responders, nearly all patients, 96 percent, in both the response-guided therapy and boceprevir/peg/ribavirin 48-week groups achieved SVR with the boceprevir response-guided therapy shorter, 28-week duration of treatment, being equally as effective as the boceprevir/peg/ribavirin 48-week treatment group.

Overall, the response of these analyses clearly demonstrate that early responders,

including black patients, can be treated for a shorter duration of 28 weeks and achieve an SVR equal to that of patients who received boceprevir plus ribavirin for 48 weeks.

Before leaving the discussion of SPRINT-2, it is important to review the data for the late responders, the other aspect of response-guided therapy. As you will recall, in the response-guided therapy group, these are patients who first have an HCV RNA that becomes undetectable after treatment week 8 and remains undetectable at treatment week 24, the yellow bar on the treatment diagram in this slide.

We compared these patients to patients in the parallel boceprevir/peg/ribavirin 48-week group who were HCV RNA detectable at treatment week 8 but who became undetectable at 24, orange bar, and continued on treatment for 48 weeks.

In the late responders, using the assigned per protocol analysis, SVRs for the response-guided therapy boceprevir regimen and the boceprevir/peg/ribavirin 48-week groups are

similar, 72 and 75 percent. However, in the FDA briefing book, the SVR rates, based on a modified FDA analysis, are 66 and 75 percent for response-guided therapy and boceprevir/peg/ribavirin 48-weeks, respectively.

The FDA analysis excludes 14 patients on the basis that these patients may have had a false positive HCV RNA during the initial treatment period from treatment week 8 to treatment week 24 and should have been assigned to the 28-week response-guided therapy regimen.

To conclude the discussion on the SPRINT-2 study, addition of boceprevir to peg/ribavirin standard of care results in a statistically significant increase in efficacy in treatment-naive patients. Using boceprevir response-guided therapy, 44 percent of patients received only 28 weeks of treatment and achieve an SVR rate of 96 percent.

Boceprevir in combination with peginterferon plus ribavirin significantly improves efficacy in the difficult to treat black patients. And for

these patients, response-guided therapy is the recommended regimen. Boceprevir in combination with peginterferon with ribavirin also improves efficacy in the difficult to treat cirrhotic patients. However, patient with cirrhosis may need 44 weeks of boceprevir treatment.

A second pivotal study in the boceprevir Phase 3 program is RESPOND-2, evaluating boceprevir in previous peginterferon plus ribavirin treatment failures. The study was a multicenter, double-blind, randomized Phase 3 study in adult patients with chronic hepatitis C genotype 1 and compensated liver disease who had previously failed treatment with peginterferon alfa-2a or alfa-2b plus ribavirin.

The objective of this study was to compare re-treatment with peginterferon plus ribavirin to each of two boceprevir-containing regimens in combination with peginterferon plus ribavirin. Peginterferon alfa-2b and ribavirin and boceprevir were administered using the same doses and regimens as in the SPRINT-2 study.

The design for this study included three treatment arms and is the same as for the previous treatment-naive study, with two exceptions: the duration of the boceprevir treatment, 32 weeks, in the boceprevir response-guided therapy arm and the timing of the futility rule, treatment week 12.

In the boceprevir response-guided therapy arm, patients received 32 weeks of boceprevir plus peg/ribavirin. Duration of therapy, 36 or 48 weeks, was determined by the detectability of HCV RNA at treatment week 8.

Patients with undetectable HCV RNA at treatment week 8 completed treatment at treatment week 36. These were the early responders for the study. Patients with detectable HCV RNA at treatment week 8 who became undetectable by treatment week 12, the late responders for this study, had their boceprevir replaced by placebo at treatment week 36 and received an additional 12 weeks of treatment, for a total of 48 weeks of treatment.

Primary and secondary endpoints and

assessment of HCV RNA for this study are the same as for the treatment-naive study; 403 patients were randomized 1:2:2 to peginterferon alfa-2b plus ribavirin or the boceprevir treatment groups, respectively. Patients were stratified by response to prior peginterferon/alfa-ribavirin treatment and HCV-1 subtype 1a versus 1b.

The study enrolled patients who are treatment failures to peginterferon plus ribavirin. Classification of non-responders is based on the patients' historic response to previous peginterferon plus ribavirin treatment. Subcategories of non-responders are based on the degree of previous interferon response.

The study included relapsers and non-responders. Relapsers are defined as patients who are HCV RNA undetectable at the end of treatment, becoming positive when therapy is discontinued. Non-responders are defined as patients who did not become HCV RNA undetectable during treatment.

Among the non-responders, the study included patients with a greater than or equal to 2 log

decrease in HCV RNA by treatment week 12, partial responders. The study excluded patients with a less than 2 log decline in HCV RNA at treatment week 12, null responders.

The decision to exclude null responders was based on a concern that for patients with a poor interferon response, that the addition of a direct-acting antiviral would result in what would be essentially monotherapy of the direct-acting antiviral and allow resistance to emerge. However, the data from the Phase 3 study support that boceprevir can be used to treat patients who have a very poor response to interferon.

The demographics of the study are similar to the treatment-naive study in that they reflect the current demographics of HCV in the United States and Western Europe where the study was conducted. The major difference in the demographics between studies is the higher number of patients with advanced fibrosis or cirrhosis in the treatment failure study, approximately 19 percent compared to approximately 9 percent in the treatment-naive

study. Overall, the baseline characteristics are similar across the three treatment groups.

The disposition of patients was included in the briefing book and so will not be discussed in detail. Patients randomized and treated in the study include 80 patients in the peginterferon plus ribavirin control, 162 patients in the boceprevir response-guided therapy arm, and 161 patients in the boceprevir/peg/ribavirin 48-week treatment group.

As in the treatment-naive study, the primary efficacy endpoint for the study is sustained virologic response, SVR in the FAS population. SVR rates in patients receiving a boceprevir-containing regimen are approximately three times higher than those in patients re-treated with peginterferon plus ribavirin.

The differences are statistically significant; 59 percent of patients in the response-guided therapy group and 66 percent of patients in the boceprevir/peg/ribavirin 48-week group compared to 21 percent of patients in the

peg/ribavirin control achieved SVR. There is a numerical difference of 7 percent between the response-guided therapy and boceprevir 48-week groups, which I will discuss later.

As in the treatment-naive study, the high SVR rates in patients receiving a boceprevir-containing regimen are achieved through both a higher response rate during therapy and a lower relapse rate. The boceprevir-containing regimens have superior SVRs compared to peginterferon ribavirin across all patient subgroups, as shown in this forest plot.

As a reminder, dots to the right of the vertical line represent a higher SVR for boceprevir versus the left of the vertical line for peg/ribavirin control. As in the treatment-naive study, these data demonstrate the strength of the overall treatment effect with boceprevir, as well as consistency of treatment effect across subgroups.

As previously discussed, there was a 7 percent in SVR between the response-guided

therapy and boceprevir/peg/ribavirin 48-week treatment groups. Additional analysis suggests that this difference is largely related to a difference in SVR in patients with cirrhosis.

As in the treatment-naive study, SVR was analyzed by presence of baseline cirrhosis versus no cirrhosis. SVR for patients with cirrhosis is shown on the left side of the slide and for patients who have no cirrhosis on the right side.

The majority of the patients in the study, approximately 85 percent, did not have cirrhosis. For patients with no cirrhosis, the SVR rates are nearly identical for the boceprevir response-guided therapy and boceprevir 48-week groups, 64 and 66 percent, respectively, and substantially higher than the peg/ribavirin control, 24 percent.

For the approximately 15 percent of patients with cirrhosis, both boceprevir-containing regimens have substantially higher SVR rates compared to the peg/ribavirin control, in which no patient achieved an SVR. However, the boceprevir/peg/ribavirin 48-week SVR rate is substantially higher than the

response-guided therapy group, 77 versus 35 percent.

Boceprevir improves efficacy in the difficult to treat patients with cirrhosis. However, these patients may require a longer duration of therapy, boceprevir plus peginterferon ribavirin for 48 weeks.

As previously noted, the majority, approximately 85 percent of patients in the study did not have cirrhosis. Therefore, the remainder of the analysis will exclude these patients to allow a better comparison of the response-guided therapy and boceprevir/peg/ribavirin 48-week groups.

This slide shows the patients' historic response to peginterferon plus ribavirin. Previous non-responders are on the left and relapsers are on the right. Both boceprevir-containing regimens have multiple-fold increases in SVR compared to the peg/ribavirin control.

For both previous non-responders and relapsers, the SVR rates within the historic

response categories are similar for response-guided therapy and boceprevir 48-weeks, 47 to 51 percent for non-responders and nearly identical, 74 and 75 percent, for relapsers.

These data demonstrate that response-guided therapy and boceprevir/peg/ribavirin for 48 weeks are approximately equally effective in patients without cirrhosis.

As for the treatment-naive study, we compared the response rates for patients in the boceprevir response-guided therapy group who were early responders, defined as HCV RNA undetectable at treatment week 8, who received 36 weeks of treatment, yellow bar, to a parallel group from the boceprevir/peg/ribavirin 48-week group who were HCV RNA undetectable at treatment week -- excuse me -- who were HCV RNA undetectable at treatment week 8 and received 48 weeks of treatment, orange bar.

Overall, as before, 44 percent of the patients met the criteria for early response. As in the treatment-naive study, the early responders

in both boceprevir-containing regimens have very high SVRs, 89 and 97 percent for boceprevir response-guided therapy and boceprevir/peg/ribavirin 48 weeks, respectively. When the patients with cirrhosis are excluded from the analysis, the SVRs for the two regimens are also extremely high, 91 and 96 percent, supporting that response-guided therapy is a viable treatment strategy for early responders.

As with the treatment-naive study, we compared the late responders from the response-guided therapy group, patients who were HCV RNA detectable at treatment week 8 and become undetectable at treatment week 12, yellow bar on the treatment diagram on this slide. We compared these with a parallel boceprevir/peg/ribavirin 48-week group who were HCV RNA undetectable at treatment week 8 but became -- excuse me -- detectable at treatment week 8 but became undetectable at treatment week 12, orange bar, and continued on treatment for 48 weeks.

The similarity of response rates between

response-guided therapy and boceprevir/peg/ribavirin 48 weeks in early responders is also observed with late responders, 80 percent of patients in the response-guided therapy arm and 73 percent of patients in the boceprevir/peg/ribavirin 48-week arm.

When the patients with no cirrhosis are also considered, the response rates for the two boceprevir regimens are similar, 85 and 78 percent for response-guided therapy and boceprevir 48 weeks, respectively, again, supporting response-guided therapy as a viable treatment strategy.

Merck is seeking a label indication for previous treatment failures that encompasses all categories of non-responders, including null responders. Therefore, the issue arises that we did not enroll historic null responders in the pivotal Phase 3 RESPOND-2 study.

The next few slides will summarize the data from the RESPOND-2 and SPRINT-2 studies that demonstrate the efficacy of boceprevir for all categories of non-responders and the new data from

the PROVIDE rollover study that is treating prospectively defined null responders. As a reminder, historical null responders are defined by their very poor response to interferon; that is, less than 2 log decline in HCV RNA at treatment week 12. Although we excluded these patients from the RESPOND-2 study, there are patients in both the RESPOND-2 and the SPRINT-2 studies with very poor interferon response that were included and treated.

The inclusion of patients with poor interferon response in the boceprevir studies can be documented in two ways. Firstly, 20 percent of the patients in the peginterferon ribavirin control in both SPRINT-2 and RESPOND-2 failed to achieve a 2 log decline in HCV RNA at treatment week 12, null responders. We would expect to find a similar number of patients in the boceprevir groups since these were randomized studies. These control patients had little or no response.

Second, both treatment week 4, less than 1 log, as outlined in the briefing document, and treatment week 12, less than 2 log, historical non-

responders, defined patients who are unlikely to respond to peginterferon plus ribavirin treatment.

Lastly, we have end of treatment results from the PROVIDE study. This is a study which includes patients from the peg/ribavirin control groups in the Phase 3 trials who, one, failed therapy with peginterferon plus ribavirin; two, met the week 12 definition of null response; and, three, who received treatment with boceprevir. This data has been shared with the FDA but not fully reviewed.

This slide shows the SVR rate in the patients in the peg/ribavirin control arm of the RESPOND-2 study who met the definition of null responder at treatment week 12. No patient achieved an SVR. Likewise, this slide shows the SVR rate in the patients in the control arm who met the alternative less than 1 log decline at treatment week 4, definition of poor interferon response. Just as with the 12-week definition, no patient achieved an SVR.

These data support that both definitions

identify patients unlikely to respond to peg/ribavirin plus ribavirin.

In contrast, in the boceprevir-containing treatment regimen using the less than 1 log week 4 definition, 33 and 34 percent of patients in the boceprevir response-guided therapy and boceprevir/peg/ribavirin 48-week groups achieved SVR.

Overall, the data shows that, one, the treatment week 4 definition of less than 1 log decline at treatment week 4 defines patients who have a poor response to interferon; and, two, clearly demonstrates that boceprevir in combination with peginterferon ribavirin can achieve SVR in these difficult to treat patients.

The findings in the SPRINT-2 were similar. In the peg/ribavirin control, SVR was 0 percent and 4 percent for the treatment week 12 and treatment week 4 definitions, respectively. These studies again demonstrate that patients who have poor interferon response by either definition rarely achieve an SVR.

As in the RESPOND-2 study, the addition of boceprevir resulted in a substantial number of patients achieving an SVR in the boceprevir response-guided therapy and boceprevir/peg/ribavirin week regimens, 28 and 38 percent, respectively.

As I had noted previously, PROVIDE is a rollover study that provides treatment with boceprevir to patients who are peg/ribavirin controls in one of the clinical studies and who failed treatment with peginterferon plus ribavirin.

We have end of treatment HCV RNA results for patients that were in the SPRINT-2 and RESPOND-2 studies who, one, failed to respond as a peginterferon ribavirin control; two, met the definition of null response, treatment week 12, less than 2 log decline; and, three, who received treatment with boceprevir for 44 weeks.

There are 38 null responder patients who have completed treatment, of whom 15 of the 38, 39 percent, are undetectable at end of treatment. On the left of the slide are the weeks of

boceprevir they've received, 44 weeks, end of treatment. On the right side of the slide, those are currently undetectable, have undetectable HCV RNA, 15 of the 38, or 39 percent. While SVR data is not available, this end of treatment response rate is consistent with the end of therapy data from the Phase 3 trials in patients with less than 1 log decline at treatment week 4.

To summarize the data, these data demonstrate that in patients with poor interferon response, that treatment week 4 definition is a good surrogate for poor interferon response and a useful alternative to the historical treatment week 12 definition. They demonstrate a broad range of treatment failure, and treatment-naive patients were enrolled in the Phase 3 boceprevir program, including hard to treat patients comparable to the conventional null definition.

We also see from these data that boceprevir added to peginterferon plus ribavirin therapy resulted in an increase of approximately 30 percent in SVR in those difficult to treat patients. Thus,

the data support our proposed indication for peginterferon plus ribavirin for use in the treatment of all previous peginterferon plus ribavirin treatment failures.

To conclude the discussion of the RESPOND-2 study, adding boceprevir to peginterferon plus ribavirin for the treatment failure population resulted in a statistically significant approximately threefold increase in SVR. Boceprevir response-guided therapy allowed a shorter duration of treatment in 44 percent of patients, the early responders, who achieved an 89 percent SVR.

Regardless of a patient's historic response classification, the addition of boceprevir substantially increase SVR, with the highest responses being observed in patients with good interferon response, such as relapsers. However, there was also a robust response in the more poorly responsive non-responders. This data supports that response-guided therapy is the optimal regimen in these populations.

Boceprevir also improves efficacy in the difficult to treat cirrhotic patients. However, patients with cirrhosis may require 44 weeks of boceprevir treatment.

In conclusion, the results of the boceprevir Phase 3 studies support that the addition of boceprevir to peg/ribavirin standard of care results in significant increases in SVR in both naive and treatment failure patients.

Boceprevir in combination with peginterferon ribavirin increases SVR rates in all subgroups of patients, including patients with a poor interferon response. And most importantly, boceprevir response-guided therapy allows the early responder to receive a shorter duration of therapy with efficacy equal to adding boceprevir to the standard peginterferon plus ribavirin 48-week regimen.

Thus, boceprevir response-guided therapy is the recommended strategy for both treatment-naive and previous treatment failure patients. However, patients with cirrhosis may need 44 weeks of boceprevir in combination with peg/ribavirin

treatment.

I would now like to introduce Dr. Clifford Brass, who will review the resistance profile and safety of boceprevir.

Sponsor Presentation – Clifford Brass

DR. BRASS: Thank you, Dr. Albrecht.

This portion of the presentation will show that the addition of boceprevir to peg/riba standard of care has a favorable benefit-risk ratio, as reflected in the profiles of resistance, adverse events, and clinical pharmacology. The use of the response-guided therapy paradigm further increases the benefit-risk ratio of boceprevir combination therapy and supports the proposed indication.

Replication of HCV viruses is dependent on an error-prone, RNA-dependent RNA polymerase. This results in a population of genetically distinct HCV particles within the population of viruses in an infected patient.

Boceprevir is a direct-acting antiviral agent that targets the HCV NS3 protease. The loss

of susceptibility to HCV protease inhibitors is associated with the selection of variants with amino acid changes in the NS3 coding region.

Variants that cause a decreased susceptibility to boceprevir are termed resistance-associated amino acid variants or RAVs. RAVs are identified in vitro and in vivo and map to the NS3 region of the HDB genome. RAVs were characterized in the pivotal Phase 3 trials at baseline, at treatment week 8, and at the time of virologic failure. Finally, RAVs are followed post-therapy to evaluate their persistence.

Putative RAVs were first identified as amino acid changes appearing in replicons during in vitro resistance selection experiments or in viruses from patients treated with boceprevir. Each of these variants was engineered into prototypical genotype 1a or 1b proteases and tested in vitro for a decreased susceptibility to boceprevir.

Variants that cause a decreased susceptibility to boceprevir were observed at 10 loci in the NS3 and are listed on this slide. The

full change in susceptibility to boceprevir differed for each variant and ranged from twofold to 300-fold in enzymatic assays in vitro.

Samples for resistance testing were taken frequently from patients enrolled in boceprevir clinical studies. Population sequence data was available for 96 percent of patients at baseline and post-baseline sequence data was available for 86 percent of patients that failed to achieve an SVR.

Viruses at the above time points were analyzed using a population sequencing method that overall detects minor variants existing in the population at a frequency of 20 percent or higher. For technical reasons, samples were sequenced only when the viral load was greater than 1,000 international units per ml. In the boceprevir pivotal studies, the sequence was obtained on the NS3 region.

The following slides show the resistance data for patients that received boceprevir plus peg/riba in the SPRINT-2 and RESPOND-2 studies.

In SPRINT-2 and RESPOND-2, RAVs were associated with virologic failure and were detected in 53 percent of all non-SVR patients. However, as the majority of patients treated with boceprevir achieved an SVR, this number represents 15 percent of all patients treated with boceprevir. RAVs that were identified in greater than 25 percent of patients with RAVs at virologic failure differed by genotype. The most common RAVs associated with genotype 1a and 1b are shown on this slide.

One of the benefits of the lead-in strategy is to allow the assessment of the peg/riba response based on HCV RNA declines at in treatment week 4 prior to receiving boceprevir, as discussed in detail in the briefing book. This allows a relationship between interferon responsiveness and the development of RAVs to be determined.

Subjects with a greater than or equal to 1 log reduction in HCV RNA at treatment week 4 are defined as interferon responsive, while subjects with a less than 1 log reduction in HCV RNA at the same time point are defined as poorly interferon

responsive.

This slide shows the percent of RAVs detected in non-SVR patients by interferon responsiveness. RAVs were detected in 69 percent of poorly interferon responsive patients compared to 31 percent of interferon responsive patients. This indicates that interferon responsiveness can influence the selection of RAVs in non-SVR subjects, most likely due to the ability of the peg/riba therapy to suppress viral replication.

RAVs were detected in 7 percent of patients with samples sequenced at baseline by population sequencing. SVR rates in these patients were similar to the majority of patients that did not have RAVs detected at baseline. Therefore, detection of RAVs at baseline alone was not predictive of treatment outcome on boceprevir plus peg/riba therapy.

In a new analysis not presented in the briefing book, we examined the persistence of RAVs in the non-SVR patients in SPRINT-2 and RESPOND-2. This slide shows the detectability of the most

common RAVs declined during follow-up. During the 6 to 14-month post-therapy period, the majority of patients had RAVs that became undetectable by population sequencing. Although different RAVs declined at different rates, shown here for the six most common RAVs, they all declined over this period of time.

To summarize, overall, the presence of RAVs at baseline was not predictive of outcome. Fifty-three percent of non-SVR subjects had viruses with RAVs detected post-baseline. In treatment failures, the most common RAVs differed by genotype and are listed here.

RAVs detected in non-SVR patients declined over time. The majority of patients did not have detectable RAVs 6 to 14 months post-therapy, but the percent decrease differed based on the RAV selected and ranged from 68 percent to 94 percent. Studies to evaluate whether RAVs returned to pre-treatment levels are ongoing, but the clinical significance of RAVs is unknown.

The addition of boceprevir to the peg/riba

standard of care was generally safe and well tolerated, with the profile of adverse events consistent with backbone therapy. The pooled safety database showed some incremental increases in a small number of events, which did not generally lead to discontinuation of boceprevir.

The safety database includes the pivotal Phase 3 studies, SPRINT-2 and RESPOND-2, and SPRINT-1, an open-label Phase 2 study in treatment-naive patients. SPRINT-1 was the first study to use the proposed regimen of peg/riba plus boceprevir, 800 milligrams TID.

In all three of these key studies, boceprevir was dosed at 800 milligrams TID for 20 weeks or more. For the integrated analysis of safety, all boceprevir-containing regimens were merged, including the response-guided therapy arms and the 48-week peg/riba/boceprevir arms. Overall, 2,095 patients are in the key studies, including 1,548 patients in the boceprevir arms, which was threefold greater than the 547 peg/riba control patients.

The majority of patients, 78 percent, received more than 24 weeks of boceprevir, and total boceprevir exposure in these three key studies was 840 patient years.

The following analysis includes all patients who received at least one dose of any study drug, whether or not they discontinued during the lead-in period, and the full study period of 72 weeks is described.

The safety profile of boceprevir combination therapy is largely a reflection of the peginterferon and ribavirin backbone, with some increases in events that are generally predictable and manageable. Nearly every subject in the key studies reported an adverse event.

Although the actual number of events varied widely due to the threefold greater number of patients in the boceprevir arms, the percentages of subjects reporting SAEs in treatment discontinuations due to an AE were similar in the peg/riba control and boceprevir-containing treatment arms.

Of the 2,095 subjects treated, eight died during the course of the key studies. Four deaths, or 1 percent, occurred in the peg/riba control arms and four deaths, which is less than 1 percent, occurred in the boceprevir-containing treatment arms. Dose reduction, primarily ribavirin dose reduction for anemia, was greater in the boceprevir arms.

The most common adverse events reported in the boceprevir/peg/riba arms are largely reflective of the known events associated with the peg/riba backbone. Most of these adverse events, highlighted in orange, occur commonly with peg/riba therapy due to the flu-like symptoms or the gastrointestinal side effects associated with peg/riba therapy. These events were reported in a similar proportion of patients in the boceprevir/peg/riba and peg/riba control arms.

Only two adverse events, anemia and dysgeusia, occur 20 percent more often in the boceprevir-containing regimens, and these will be discussed as events of special interest. Nausea,

diarrhea and neutropenia are the only other common events listed here, which are 5 percent greater when boceprevir is added to the peg/riba standard of care.

Events of special interest include events increased on boceprevir or expected to be increased with some ketoamide protease inhibitors.

Three broad areas are examined as events of special interest: hematologic events, dysgeusia and rash. The increased hematologic events occurring with boceprevir use, primarily an increase in anemia, appear to be class effects associated with protease inhibitors of the ketoamide class.

In addition, the incidence of dysgeusia, an altered sense of taste, was specifically increased with the addition of boceprevir. Skin rash, an event of special interest based on its association with ribavirin treatment and its increased occurrence with another drug in the same ketoamide class was not increased in the pooled boceprevir arms.

An approximately 3 gram per deciliter drop in hemoglobin concentration is a well recognized side effect of treatment with peginterferon and ribavirin. Interferon is a bone marrow suppressant, and ribavirin causes a dose dependent hemolysis, which is the primary driver of this drop in hemoglobin.

Boceprevir as a single agent did not cause a drop in hemoglobin in either animal studies or in a Phase 1 monotherapy study. When healthy male adults were treated with boceprevir for up to 57 days, no effects were demonstrated on red cell production, survival or destruction, or on markers of anemia. However, when boceprevir is added to peg/riba therapy, it causes an incremental drop in hemoglobin of approximately 1 gram per deciliter.

The management of anemia for patients receiving boceprevir combination therapy is identical to that for anemic patients receiving peginterferon plus ribavirin standard of care. The incidence of discontinuation from therapy because of anemia is similarly low, at approximately 1

percent in both the peg/riba control and boceprevir experimental arms. Anemia is transient as hemoglobin returns to baseline post-therapy in control and experimental arms.

This slide shows the mean hemoglobin concentration on the Y-axis during 48 weeks of treatment and 24 weeks of follow-up, X-axis, for patients in the control, white line, and boceprevir experimental arms, yellow line, in the key safety studies. The pattern of mean hemoglobin concentration over time, with a return to baseline on follow-up, was similar in the boceprevir/peg/riba arms and the peg/riba control arms.

Boceprevir exacerbates the hemoglobin drop caused by peginterferon ribavirin therapy, as reflected in the nadir hemoglobin levels on treatment of patients in the control arms, white bars, and boceprevir/peg/riba arms, yellow bars, which are displayed here according to the WHO toxicity grade. Three percent of patients in the boceprevir combination arms had WHO grade 3 or 4

anemia and hemoglobin of 8 grams per deciliter or less compared to 1 percent in the pegloticase-riba control.

Anemia was managed in the key trials with the same tools used to treat anemia with peg/riba therapy in clinical practice today, ribavirin dose reduction and/or treatment with erythropoietin, also referred to as EPO. Guidelines for the use of EPO were provided in the study protocols and were based on product inserts for erythropoietin use in other disease states. The decision to use EPO and implement these guidelines was based solely on investigator judgment.

Among anemic patients, both ribavirin dose reduction and erythropoietin use was common. When aggregated, more patients receiving boceprevir, 25 percent, had a ribavirin dose reduction compared to control at 12 percent. Similarly, 38 percent of patients in the experimental arms were treated with erythropoietin to ameliorate their anemia compared to 19 percent in the control arms.

Erythropoietin utilization was greater than

noted in clinical practice or previous trials. This may relate to the fact that it was provided by the sponsor upon physician request. Overall, the management strategies for anemia were similar between treatment and control arms, reflecting the standard management of anemia in subjects receiving combination therapy with peg/riba, as described in the VA Guidelines for Health Care Providers.

There were no significant increases in events that are associated with EPO use in other chronic diseases, such as hypertension, thrombosis or cancer. However, there was00:15:39 one case reported as antibody-mediated pure red cell aplasia. A recent update now reveals that this patient fully recovered with immunosuppressive therapy.

Although anemia can be a safety issue, paradoxically, it also seems to be a marker of increased virologic response with two-drug therapy, as previously demonstrated in the IDEAL trial, a 3,000-patient study of treatment-naive patients.

This slide shows the SVR rate in all three

arms of SPRINT-2 and RESPOND-2 displayed for patients who became anemic on therapy, stippled bars, and patients in the same arm who did not become anemic, solid bars. For all three arms in both studies, patients developing anemia on boceprevir combination therapy or control treatment had higher SVR rates than patients who did not develop anemia.

Based on exploratory analyses, these high SVR rates in anemic patients were maintained independent of the interventions used to manage anemia. In both SPRINT-2 and RESPOND-2, similar high levels of SVR were achieved in anemic patients managed with ribavirin dose reduction alone or EPO treatment with or without ribavirin dose reduction.

Anemia is captured in these studies either by a laboratory report of a hemoglobin less than 10 grams per deciliter or was reported by the investigator as an adverse event. The rates of anemia reported as an adverse event were 29 percent in the control arms and 49 percent in the boceprevir arms.

Anemia was generally manageable. Approximately one-quarter of all boceprevir-treated patients required dose modification for anemia, but only 3 percent were transfused, and only 1 percent reported SAEs of anemia. Ribavirin dose reduction and/or erythropoietin use were effective in maintaining subjects on therapy, as only 1 percent required treatment discontinuation for anemia.

There were also increases in neutropenia on boceprevir. Peginterferon plus ribavirin leads to a decrease in neutrophil counts during treatment. An incremental effect of boceprevir in neutrophils resulted in increased rates of grade 3 and 4 neutropenia and absolute neutrophil count of less than 750 in 500 million cells per liter, respectively, when compared to peg/riba control.

Neutropenia, as reported by the investigator, was managed in the key trials primarily by peginterferon dose reduction. Granulocyte colony stimulating factor, GCSF, was also occasionally used, but the drug was not provided by the sponsor. GCSF use was low but

higher in the boceprevir/peg/riba arms compared to the peg/riba control at 9 percent and 6 percent, respectively.

Eight percent of patients in the control arms and 13 percent of patients in the boceprevir arms dose reduced the study drug for neutropenia. Zero and 1 percent of patients in the control and experimental arms, respectively, discontinued treatment for neutropenia.

As discussed in the briefing book, there were five cases of grade 3 and 4 neutropenia temporally related to severe infections or cases that the investigators judged to be life-threatening neutropenia. All resolved with the antibiotics and/or cessation of boceprevir/peg/riba therapy.

There were also incremental increases in thrombocytopenia associated with the addition of boceprevir at the standard of care. Interferon causes a decrease in circulating platelets, sometimes leading to thrombocytopenia.

When boceprevir was added to the

peginterferon plus ribavirin backbone, there was an increase in subjects with thrombocytopenia during therapy. Grade 3, less than 50 x 10 to the 9 cells per liter was increased from 1 percent in the control to 3 percent with boceprevir combination therapy. No severe events were reported in association with thrombocytopenia.

Dysgeusia, although clearly increased with the addition of boceprevir to the peg/riba backbone, was mild, transient, and rarely required medical intervention. Some of the verbatim terms coded to this event included metallic taste in mouth, earthy aftertaste, and bitter taste.

While 37 percent of patients in the key studies experienced dysgeusia, less than 1 percent dose reduced or discontinued drug due to dysgeusia. Dysgeusia was typically mild. Only 1 percent were reported to be severe. None were serious. Dysgeusia events tended to begin early in the course of treatment and were associated with gastrointestinal symptoms, such as nausea, vomiting, and diarrhea.

Rash, mainly related to ribavirin use, is fairly common with peginterferon and ribavirin therapy. Overall, the rate of rash was similar in the control arm and the boceprevir regimens, 27 percent and 30 percent respectively. Rash was typically described as being consistent with ribavirin rash without mucosal involvement. There were no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis addressed.

Treatment-related rash AEs, such as pruritis, occurred in similar proportions of subjects in the boceprevir-containing and peg/riba control arms. Rashes were generally mild to moderate in severity and were usually managed with oral antihistamines and topical corticosteroids.

One percent or less of subjects required dose reductions or study drug discontinuation due to rash, and only one patient in the boceprevir/peg/riba arms reported rash as an SAE. This was an erythematous rash that did not require hospitalization and resolved on full doses of study drugs.

Safety was examined in subgroups, including age, gender, race, BMI, and co-morbid conditions, such as cirrhosis and hypertension. The degree of anemia was increased in the elderly, defined as those greater than 65 years of age, as well as women and cirrhotics. All three groups had lower baseline hemoglobin.

Cirrhotic subjects also experienced relatively more thrombocytopenia compared to non-cirrhotic subjects. All these observations have been made previously for peg/riba standard of care treatment. There were no clear differences in adverse events reported by race.

Response-guided therapy by decreasing treatment duration of all three study drugs offers several safety advantages. Dr. Albrecht has already shown that the increase in efficacy over control for boceprevir RGT arm was similar to that of the 48-week boceprevir/peg/riba arm.

In particular, SVR rates were very high in all patients with an early response to therapy. The RGT arms were designed to limit drug exposure,

particularly in these early responders. Response-guided therapy is anticipated to reduce both discontinuations due to adverse events and the duration of adverse events.

The safety advantages of RGT can be evaluated by comparing safety in early responders in the RGT arm to the corresponding early responders in the peg/riba/boceprevir 48-week arm. Because of this 20-week difference between short therapy and long therapy, this safety difference is most obvious in the naive study, SPRINT-2, as shown here. Mean boceprevir/peg/riba exposure was reduced 37 percent and mean EPO exposure was reduced 46 percent in the early responders in the RGT arm.

Although there were similar rates of SAEs, there were fewer study drug discontinuations for adverse events, 9 percent compared to 17 percent in the early responders in the RGT arm compared to the corresponding early responders in the boceprevir/peg/riba 48-week arm. And the rate of severe anemia was reduced from 5 percent to

1 percent with the shorter therapy.

Additionally, the length of an adverse event when it occurred was decreased for early responders in the RGT arm. For example, in patients who developed moderate to severe depression, a side effect associated with interferon therapy, the mean length of depression was 16 weeks for patients in the RGT arm and 30 weeks for the corresponding early responders in the boceprevir/peg/riba 48-week arm.

As previously shown for hemoglobin, all hematologic parameters returned to normal after discontinuing therapy. The advantage of the shorter duration of therapy in the early responders in the RGT arm compared to those early responders in the boceprevir/peg/riba 48-week arm is shown here.

Hemoglobin levels normalize after therapy is completed at treatment week 28 for patients in the RGT arm, yellow line, compared to the continued lower hemoglobin of those still on therapy in the 48-week regimen, orange line.

Similarly, neutrophils counts normalize quickly for early responders in the RGT arm after therapy is completed at treatment week 28, yellow line, compared to the continued lower neutrophil counts of the corresponding early responders still on therapy in the 48-week treatment regimen, orange line.

The Phase 3 trials confirmed the use of boceprevir 800 milligrams TID as an efficacious and safe dose to be used in addition to the current standard of care, peginterferon and ribavirin. The clinical pharmacology of boceprevir supports this regimen with no dose adjustments required for special populations.

Absorption of boceprevir is rapid, with less than dose proportional exposure and no accumulation. Food increases exposure to boceprevir by 40 to 60 percent, regardless of meal type. Boceprevir is extensively metabolized by two distinct pathways, via aldoketorereductase mediated reduction and via CYP3A4 mediated oxidation.

The half-life is approximately three and a

half hours, with the majority of boceprevir excreted hepatically and focally. Boceprevir is a strong, reversible inhibitor of CYP3A4 and is not a CYP P450 isoenzyme inducer.

Merck has conducted several investigations to characterize the drug-drug interactions with boceprevir. Since the biotransformation and clearance of boceprevir involves two different enzymatic pathways, boceprevir is less likely to be a victim of drug-drug interactions with concomitant medications that affect either of these pathways. Investigations of drug-drug interactions with boceprevir do not show clinically relevant changes in boceprevir exposure that would require a dose or schedule adjustment.

In clinical trials, co-administration of aldoketorereductase inhibitors, such as ibuprofen or diflunisal, did not increase exposure to boceprevir. The published literature on known inhibitors does not show evidence of saturation of aldoketorereductase isoforms to an extent that has observable clinical effects.

Co-administration of boceprevir with strong CYP3A4 and PGB inhibitors, such as ketoconazole or CYP3A4 inducers, such as efavirenz, while showing some variability, did not change the exposure to boceprevir to a clinically concerning extent. In addition, boceprevir will be administered with standard of care and no interaction has been observed between boceprevir and peginterferon alfa-2b or ribavirin.

Since boceprevir is a strong inhibitor of CYP3A4, drugs metabolized primarily by CPY3A4, such as midazolam, may have increased exposure when administered with boceprevir. This could increase or prolong therapeutic and adverse effects, and dose adjustment and/or clinical monitoring of the co-administered drug may be warranted.

Sub-analysis of safety in the Phase 3 trials when boceprevir and standard of care was administered concomitantly in the presence or absence of specific classes of medications, such as CYP3A4 substrates, including oral benzodiazepines or CYP3A4 inhibitors, such as the azoles, suggest

that, in general, the safety profile was similar. However, a number of additional studies examining drug-drug interactions for drugs metabolized by CYP3A4, including methadone and oral contraceptives, are being prepared.

No clinically meaningful change in exposure to boceprevir was observed in subjects with hepatic impairment or renal insufficiency or when analyzed for specific demographic factors, such as gender or race. Boceprevir was not associated with clinically relevant effects on cardiac conductions as assessed in a multiple dose thorough QT study.

To summarize, the addition of boceprevir to peg/riba standard of care is safe and generally well tolerated. Treatment duration of boceprevir/peg/riba therapy is not limited by toxicity and safety data available for 44 weeks of boceprevir administration. The safety profile of boceprevir combination therapy largely reflects the known profile of peginterferon and ribavirin with incremental hematologic effects and dysgeusia, which are manageable.

No dose adjustment of boceprevir is required when co-administered with other medications or in the treatment of special populations, including those with hepatic impairment. Response-guided therapy leads to decreased exposure to all three study drugs for nearly half the patients.

I would now like to introduce Dr. Keith Gottesdiener, who will review for you the risk-benefit of boceprevir combination therapy.

Sponsor Presentation – Keith Gottesdiener

DR. GOTTESDIENER: Thank you.

Boceprevir added to standard of care has a positive benefit-risk ratio, with increased SVR rates seen in every population treated and no new safety concerns that limit the duration of therapy.

The current standard of care for chronic genotype 1 HCV infection is associated with low rates of SVR, particularly in certain patient populations. There is a need for therapies that increase rates of SVR without adding new safety concerns. Boceprevir, a first generation HCV protease inhibitor, meets this need.

In pivotal studies of treatment-naive and treatment failure patients, boceprevir increased SVR rates nearly twofold and threefold, respectively, compared to standard of care and also decreased relapse rates.

Improved SVR rates were demonstrated in all study populations, with substantial improvement in the most difficult to treat groups, such as black patients and those with advanced hepatic fibrosis or cirrhosis. Response-guided therapy also offered a shorter duration of therapy for nearly half of patients.

I've shown in the briefing book the durability of SVR has been documented in follow-up studies that have been conducted for more than two years. No cases of late virological relapse were identified.

Consistent with ICH guidelines for the evaluation of drug safety, the clinical development program for boceprevir provides a safety database that is extensive both in terms of size and duration. Overall, the addition of boceprevir to

the peginterferon and ribavirin standard of care has been generally well tolerated, with low discontinuation rates due to adverse experiences. No specific safety issues have been identified that would preclude the use of boceprevir for the proposed indication.

The addition of boceprevir to interferon and ribavirin results in a safety profile that largely reflects that of standard of care therapy alone. Incremental adverse experiences are generally monitorable, manageable, and reversible. And safety has been demonstrated with boceprevir treatment for up to 44 weeks, and there are no specific toxicities that limit duration of therapy.

Anemia is a known adverse event associated with standard of care treatment of HCV. Boceprevir added to standard of care causes an additional decrease in hemoglobin of about 1 gram per deciliter, but this can be managed with the current tools used to manage anemia with standard of care therapy; in other words, ribavirin dose reduction and/or erythropoietin. Both strategies are

associated with increased rates of sustained virological response. Of note, there were smaller effects on other hematological parameters, such as neutrophils.

Boceprevir affects the plasma concentration of drugs which are metabolized by CYP3A4; and so concomitant administration of drugs that are CYP3A4 substrates and have a narrow therapeutic index should be avoided. Additional studies we'll be initiating shortly to complete the profile for potential drug-drug interactions. Boceprevir is contraindicated in pregnancy due to its required use with ribavirin, a known teratogen.

HCV-resistant associated variants, or RAVs, occur in many non-SVR patients. Long-term, ongoing follow-up studies show that RAVs diminish over time, but the clinical implications of RAVs are unknown.

Some of these risks persist for as long as therapy is continued, so an early futility rule would be a benefit. This might be particularly important for treatment-naive patients, where, in

SPRINT-2, the FDA and the sponsor agreed on a futility rule at treatment week 24, at which time patients with detectable HCV RNA were discontinued.

With the help and the support of the FDA, the sponsor has just completed an extensive post hoc evaluation of alternative early futility rules.

Now, we will briefly present our proposal for which the FDA is in general conceptual agreement, although the details are still under discussion. This slide is not in your briefing booklet, but the proposal can be explored in the Q&A, if desired.

The goals of these evaluations were, one, to preserve SVR rates for those patients who might achieve SVR with further therapy; in other words, not to discontinue patients who might achieve an SVR.

Number two, stop therapy early in patients unlikely to ever achieve SVR with continued therapy; in other words, to prevent the development of RAVs and adverse experiences in patients who have little, if any, chance of achieving SVR. And

three, to harmonize futility rules across populations to reduce the complexity of the treatment regimens.

The proposed futility rule would discontinue treatment if patients had HCV RNA levels greater than 100 units at treatment week 12 or detectable HCV RNA at treatment week 24. In order to minimize confusion and based on the public health benefit of having a consistent rule for both populations, this rule will be similar for both treatment-naive and treatment failure patients.

This rule meets the goals above and would identify a substantial number of patients who would meet early futility, thereby minimizing patients who would receive continued therapy without benefit but would also preserve SVR rates.

An early futility rule is one approach to maximizing the benefit-risk ratio for boceprevir. The use of a response-guided therapy paradigm is a complementary approach that further increases the benefit-risk assessment of boceprevir combination therapy.

Early responders, representing approximately half of all patients, attained similar and very high SVR rates when treated with a short RGT regimen versus 48 weeks of therapy in the trials for both treatment-naive and treatment failure patients. Additionally, with RGT, the risks of therapy are less due to shorter exposure to all three drugs, boceprevir, peginterferon, and ribavirin. However, based on limited data available from these trials, patients with cirrhosis should receive 44 weeks of boceprevir.

After very recent scientific discussions with the FDA, the sponsor agrees it would be appropriate to recommend a duration of boceprevir therapy that is greater than 24 weeks in treatment-naive late responders. This is reflected on this slide, which also is not included in your briefing booklet.

Therefore, the proposed dosage administration should be, number one, all patients will initiate treatment with four weeks of lead-in with peginterferon/ribavirin, after which

boceprevir at 800 milligrams TID will be added to the regimen; number two, response-guided therapy would be the optimal regimen for most patients; number three, after the lead-in, early responders treatment-naive patients would receive 24 weeks of additional boceprevir/peg/riba, while early responders treatment failure patients would receive 32 weeks of additional boceprevir/peg/riba.

After the lead-in, late responders, in this case, both naive and prior treatment failure patients, would receive 32 additional weeks of boceprevir/peg/riba, followed by 12 weeks of peg/riba alone.

As mentioned previously, cirrhotics, defined either clinically or histologically, would receive a longer duration of therapy, lead-in plus 44 weeks of therapy, triple therapy.

Should the advisory committee and the FDA agree that boceprevir can be used to treat historical null responders? Null responders would also receive longer duration of therapy, lead-in plus 44 weeks of triple therapy.

Overall, the benefits of adding boceprevir to the peg/riba standard of care provide a favorable benefit-risk assessment and support the proposed indication for boceprevir. Boceprevir is indicated, in combination with pegylated interferon and ribavirin, for the treatment of HCV genotype 1 infection in previously untreated and previous treatment failure adult patients with compensated liver disease.

Genotype 1 is the most common form of HCV infection in the U.S. and in Western Europe. The addition of boceprevir to peginterferon/ribavirin standard of care represents the next major advance in the treatment of the disease.

Thank you very much for your kind attention. And I'll invite Dr. Jan Albrecht back to the podium, who will respond to clarifying questions.

Clarifying Questions from Committee to Sponsor

DR. CARGILL: Thank you very much.

Clarifying questions from the committee for the sponsor? Dr. Ellenberg?

DR. ELLENBERG: Could you clarify for me the

follow-up procedures for subjects, the follow-up for safety, including people who were taken off after the lead-in, including people who were taken off after 12 weeks, including people who were taken off because of adverse events, whatever?

I would like to know what the protocol was for following for safety and whether all these subjects continue under follow-up for safety.

DR. ALBRECHT: The protocol specified that patients who discontinued early or were taken off for any reason would enter a six-month follow-up period. So if a patient discontinued therapy at 12 weeks, for example, they would go then into the 24-week or six-month follow-up period.

In addition, the study that we mentioned in the briefing book, the long-term follow-up study, all patients, whether responders, non-responders, who completed the six-month follow-up period were invited to join a three-year long-term follow-up study in which they're being followed both for safety, severe adverse events, and they're also being followed for HCV RNA, either loss of response

or presence of HCV RNA.

DR. ELLENBERG: So if they were discontinued, they have a six-month follow-up period. And if they didn't discontinue and completed the study, then how long were they -- was follow-up also discontinued after six months?

DR. ALBRECHT: The same criteria, that the patient completed the study, they had a six-month follow-up period, at which time they were invited to join the three-year follow-up study.

Not all patients accepted to join the three-year follow-up study, I should comment.

DR. CARGILL: Dr. Knodell?

DR. KNODELL: I was just wondering. Maybe in Europe they have breakfast at 6:00 and dinner at 2:00 or lunch at 2:00 and dinner at 10:00, but in the United States, that would be unusual timing for meals. And since you think that food is important, how important is this QA hour dosing in terms of efficacy? Because that might be hard to enforce in the United States.

DR. ALBRECHT: The food that the patient was

asked to take did not need to be an entire meal. It could be just simply a cracker or a small snack.

We suggested that they dose in a 7 to 9-hour window, so it was essentially three times a day dosing. And we also did look at the effect of adherence to the boceprevir dosing regimen on the SVR rate, and what we found was that in a group of patients who were generally adherent to their dosing overall, their dosing schedule, that the adherence to the strict 7 to 9-hour window did not have a substantial effect on the SVR. However, we're not recommending that the drug be dosed other than the 7 to 9-hour window that was used in the clinical trials, because that's what we studied.

DR. CARGILL: Dr. Clay?

DR. CLAY: I had another question, but I want a follow-up to his question, because I think what he's getting at is forgiveness in a dosing regimen of TID or every eight hours. And your response was that if they were late with their medicines, it didn't really make a difference.

Did you capture in the clinical trials what

your definition of late constituted?

DR. ALBRECHT: Yes. The data that I just referred to, we used an electronic dosing diary that the patient completed every day, and we collected the fact that they not only took their drug, but when they took it. And when we looked at patients who were generally adherent in taking their drug, meaning that they took their three drugs on the daily schedule they were supposed to, we saw that in the patients that were, say, 80 percent adherent to the seven --

DR. CLAY: No, I understand that, but you're talking about total daily. I'm talking about hours; was there a window of hours?

Is that what you were getting to?

DR. ALBRECHT: Yes.

DR. CLAY: Okay. I'm sorry, apologize for interrupting.

DR. ALBRECHT: We actually tracked whether they took their dose according to the hours, the 7 to 9-hour window. And what I'm saying, in those people that were generally adherent taking their

drug, they were also adherent to the 7 to 9-hour window. But there were some cases where patients didn't adhere to it, and it doesn't appear to make a difference.

DR. CLAY: And generally refers to what percentage? I mean, we're HIV people. We're used to talking adherence rates here. So that's why I'm asking.

DR. ALBRECHT: Could I have slide 2634, please?

DR. CLAY: I knew you'd have it.

DR. ALBRECHT: This is the adherence to the boceprevir dosing schedule. If you'll look at the left panel of the screen, it's the proportion of time they were adherent to the 7 or 9 hours. And this is the SVR in the patients that we were tracking. And as you can see, the SVRs tend to be very similar, someplace between 60 and 70 percent.

DR. CLAY: Thank you. I apologize, but my original question was you mentioned the drug is broken down and you give the impression it's equally between the CYP3A4 pathway and the AKR

pathway. And I see from a recent publication from Merck that it's AKR1C2 and AKR1C3. And I'm curious if you have looked at the expression difference in black patients versus non-black patients in your trial to see if that factored into your response rates, because you get two active metabolites. You get M28 and M31 and the activity level of those.

I'm just wondering if you've looked at that.

DR. ALBRECHT: Could I ask Dr. Claudia Kasserra from clin-pharm to answer the question, please?

DR. KASSERRA: We have not conducted an analysis of the different AKR isoforms in different subpopulations.

DR. CLAY: Because it's in the same family as NADPH, which may have some role in the anemia which you talked about. You saw good SVRs in people with anemia. So I'm just -- it's all tied together. It's all one person. Thank you.

DR. CARGILL: I'm going to pick up, as the chair, with some additional questions. Beginning with your slides in 89, looking at some of the

hematological profile consequences, do you have those also broken out by race, as these cohorts are lumped for this data?

[Pause.]

DR. CARGILL: If you'd like, we can come back to that later since it looks like --

DR. ALBRECHT: Could we come back to that one in just a moment?

DR. CARGILL: That's fine. But I do want to leave that question standing on the table.

DR. ALBRECHT: We have it. I'm sorry. It took us a minute to get the slide up.

DR. CARGILL: That's fine. You have it?

DR. ALBRECHT: Slide 860, please. This is the same slide that we showed you for the overall hemoglobin. This is broken out on the left panel. This is the WHO grading. On the left panel is the non-black and on the right panel is the black. As you can see, there are much smaller numbers among the black patients, but there essentially is really no difference between the black and the non-black with the hemoglobin nadirs that we saw.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: Thank you.

I have two questions. The first one is that your definition of early response or what prompted you to use response-guided therapy varied, whether the patients were naive or had prior non-response.

In the naive, it was negative HCV RNA from weeks 8 through 24, and in the patients who did not have a -- who would had previous treatment, it was 8 through 12.

Can you clarify that that's correct, first of all, and why you chose to make those different from the patients who were naive versus patients who had a prior treatment to non-response?

DR. ALBRECHT: Yes, that is correct, and the reason being the futility rule. The futility rule was treatment week 24 in the treatment naïve, and the futility rule in the previously treated patients was treatment week 12. So if a patient became HCV RNA negative at treatment week 8, they were required to remain that way all the way to the

futility rule, when we allowed them to either stop or go on.

In the previously untreated patients, the futility rule was at treatment week 12. And in the study, a patient could come out at treatment week 12. So the patient was required to be HCV RNA negative at treatment week 12 and then was rechecked, if he passed that criteria, at treatment week 36, when the decision was made whether they go to 48 weeks or 36 weeks.

DR. STRADER: And the futility rule at treatment week 12 for patients who had a prior response -- I'm just curious, because you make an argument about including null responders, because you claim that there's no real -- that people who do not achieve HCV RNA negativity in the first four weeks, that there's not a big difference between those.

So I'm curious as to why people who had prior response had to stop at treatment week 12 as opposed to 24.

DR. ALBRECHT: The futility rule for the

previously treated patients was based on a large study that was published by Poniard about two or three years ago in which we re-treated patients who had previously failed therapy with peginterferon plus ribavirin. And when we ran that study, what we determined was that if a patient had previously been treated did not respond by treatment week 12, it was highly unlikely that they would respond. And we selected the treatment week 12 futility rule based on that study. And, actually, that is a labeled indication.

DR. STRADER: Okay. In your study looking at blacks versus non-blacks, the numbers are -- it seems to be in each treatment group probably fivefold as many non-blacks as blacks. I assume you did some sort of calculation to determine what the number of blacks in each group would need to be in order to determine whether your differences in response were significant or not; is that correct?

DR. ALBRECHT: That's correct. We enrolled the two cohorts separately because we wanted to assure ourselves that we would have enough blacks

in the study to be able to look at it and hopefully achieve a statistically significant difference.

This was a multinational study conducted in other countries in addition to the United States, and, of course, when we go overseas, and particularly Western Europe, we don't accrue very many black patients. So we enrolled the non-black cohort and the black cohort separately to assure that there would be an adequate number of patients. And as you saw, the deltas were statistically significant between the controls and the treated groups.

DR. STRADER: So that the 50 patients in each group or thereabouts was considered to be enough to be able to determine a difference.

DR. ALBRECHT: We had been able to determine, based on our Phase 2 study, that we could have an expectation that the differences in response rates would be quite large, and what was how we decided on our sample sizes.

DR. CARGILL: We will now take a 15-minute break, but let me just first make sure that I

assure the panel members who had raised questions that we're not going to forget. You are definitely going to come back to them.

In addition, we'll also have Dr. Van Dyke introduce himself, since he's been able to join us.

So, please, before you leave, especially panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or any members of the audience. We will resume promptly at 10:30. Thank you.

(Whereupon, a recess was taken.)

DR. CARGILL: We are going to resume the meeting of the advisory panel. However, first, we would like to have Dr. Van Dyke introduce himself, as he was not here at the beginning of our meeting.

DR. VAN DYKE: Good morning. I'm Dr. Russell Van Dyke from the Department of Pediatrics, Tulane University in New Orleans. Unfortunately, New Orleans doesn't have a whole lot of flights and mine was canceled last night. So I had to catch an early one this morning. So I apologize for being late.

DR. CARGILL: Welcome.

Again, just to repeat that we will resume the questions this afternoon. We'll pick up so that the advisory panel members who did not have a chance to ask a question or have additional questions, we will continue at that time.

We will not proceed with our presentation from the FDA. I would like to remind our public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

FDA Presentation – Poonam Mishra

DR. MISHRA: Good morning. Today, Dr. Jeffrey Florian and I will be presenting the FDA analysis for boceprevir on behalf of the review team. This presentation will include the key safety and efficacy results and issues. I will try to focus only on the analysis where FDA has noted some differences from those of applicant and will not include the topics which have already been covered in the applicant's presentation earlier

today.

I will first start with the safety of boceprevir, focusing on anemia and other bone marrow suppressive effects. Then I will go over some of the evidence data currently available for boceprevir.

I will briefly go over the key terms and the trial designs to rearticulate the difference in the duration of therapy and the response-guided therapy arms in the two Phase 3 trials. I will discuss the primary efficacy results and pertinent subgroup analysis. Then Dr. Florian will discuss the issue of proposed indication in non-responders and optimal duration of therapy in treatment-naive late responders.

The most notable safety concerns with boceprevir are hematologic adverse events, mainly anemia, and to a lesser extent, neutropenia and thrombocytopenia.

The two Phase 3 trials, which have been analyzed for hematologic adverse events include SPRINT-2, done in previously untreated subjects. I

will also be referring to these subjects as treatment naive during my presentation today.

RESPOND-2 was done in subjects who had failed the previous course of pegylated interferon and ribavirin therapy. I will also be referring to these subjects as treatment-experienced during my presentation.

Please note that the sponsor also pulled the data from the Phase 2 open label trial, SPRINT-1 in treatment-naive subjects; hence, the analysis presented here may differ from those of the applicant's presentation earlier.

Anemia was reported as an adverse event in 52 percent of boceprevir-treated subjects compared with 30 percent of controls; that is, treated with pegylated interferon and ribavirin therapy, also referred to as PR. In these trials, investigators were advised to intervene when hemoglobin concentrations fell to 10 grams per deciliter or lower. The definition of an anemia adverse event included any laboratory value resulting in an intervention; hence, anemia adverse event reporting

was linked to the appearance of an intervention for anemia management.

This table shows an analysis of number and proportion of subjects who reached hemoglobin levels of less than 10 grams per deciliter and less than 8.5 grams per deciliter in the Phase 3 trials. A higher proportion of boceprevir-treated subjects compared to those subjects who received PR experienced hemoglobin levels of less than 10 grams per deciliter or less than 8.5 grams per deciliter in the Phase 3 trials, as shown in this table.

Anemia was reported as a serious adverse event in 12 boceprevir-treated subjects compared to one subject in the PR control arm. Anemia resulting in drug discontinuation, dose reduction, or dose interruption was also higher in the boceprevir-containing arm compared to the PR control arm, shown in the rows below.

Before I discuss any further, I would like to point out some of the challenges in the assessment of anemia in these trials. Assessment of anemia was confounded by baseline hemoglobin

values. Subjects with lower baseline hemoglobin had higher rates of nadir hemoglobin less than or equal to 10 grams per deciliter. These subjects also had more anemia adverse events reported.

Subjects with lower baseline hemoglobin had higher rates of interventions for anemia management. Subjects with lower baseline hemoglobin also had smaller magnitude of hemoglobin decline, and this I will discuss a little further.

Boceprevir-treated subjects experienced additional decline in hemoglobin. Mean hemoglobin decline beyond that seen with the PR arm was approximately 1 gram per deciliter. In some subjects, additional hemoglobin decline was greater than 1 gram per deciliter. However, assessment of risk by absolute maximum hemoglobin decline is difficult to interpret because of differential post-baseline interventions for anemia management in these trials.

This graph shows the mean decline in hemoglobin by treatment arm and visit. The X-axis denotes treatment visit and the Y-axis represents

hemoglobin decline. If you focus your attention on the left side of the graph, you will see that all arms had an initial decline in hemoglobin during the first four weeks of lead-in therapy with pegylated interferon and ribavirin, and the magnitude of decline is similar in all arms.

Boceprevir was added on at treatment week 4 and, as you can see, there was an additional decline in hemoglobin in boceprevir-containing arms, shown below the graph, whereas the red line shows the control arm.

You can see that in the treatment-naive trial, boceprevir was stopped in the RGT arm at week 28 and hemoglobin values returned to the same mean level as that with the PR alone. Similarly, when boceprevir was stopped in the RGT arm of the treatment-experienced trial, hemoglobin returned back to the PR level. Hemoglobin values returned to baseline values after all the study drugs were discontinued.

This graph shows the mean hemoglobin decline in subjects with baseline hemoglobin less than or

equal to 14 grams per deciliter compared to those with baseline hemoglobin greater than or equal to 16 grams per deciliter.

As shown in the graph on the left side, subjects with lower baseline hemoglobin values, that is, less than or equal to 14 grams per deciliter, the magnitude of additional boceprevir-associated hemoglobin decline was lower than those in subjects with baseline hemoglobin greater than or equal to 16 grams per deciliter, as shown in the graph on the right. This could be partly due to the early interventions for anemia in subjects with lower baseline hemoglobin.

These figures show the exposure-response relationship for anemia. An upward trend of increasing incidence of anemia was observed with increasing boceprevir AUC in the PK population. However, this trend was not significant. A significant relationship between incidence of anemia and ribavirin AUC was observed in the PK population receiving triple therapy.

In Phase 3 trials, as shown in our

background document, a shallow and non-significant relationship was identified between boceprevir exposure and SVR. A non-significant, but upward trending relationship between ribavirin steady-state AUC and SVR was also observed. These data also suggest that improvement in SVR rates in subjects who develop anemia compared to those who did not develop anemia during treatment may be related to higher ribavirin exposures.

Use of erythropoietins as stimulating agents, also referred to as ESAs, was allowed for the management of anemia in these trials at the investigator's discretion. This slide shows that the proportion of subjects receiving ESA was higher in the longer duration boceprevir treatment arms compared to response-guided therapy arms. This pattern continued with varying ESA treatment duration as shown in the table. Overall, ESA use was higher in the boceprevir treatment arms than the PR control arm.

ESAs are not FDA approved for the treatment of anemia in patients with chronic hepatitis C.

ESA use in itself may potentially pose an additional safety risk, the extent of which has not yet been fully described. ESA use has been associated with increased incidence in thromboembolic events. There were a few thromboembolic events reported in these trials, including a case of arterial thrombosis in one subject. A case of pure red cell aplasia, which is a rare erythropoietin side effect, was also reported in one subject during the follow-up period.

Some adverse events which may represent clinical manifestations of anemia, such as dyspnea, exertional dyspnea, dizziness, and syncope were reported more commonly in the boceprevir-containing arms compared to control. Other adverse events of interest, such as myocardial infarction, myocardial ischemia, cerebral accident or ischemia, were reported too infrequently in these trials to assess differences in proportions between the arms. Trials were not designed to specifically assess incidence of symptoms and events associated with

anemia.

This table shows that dyspnea, dizziness and syncope were numerically more frequent in boceprevir-containing arms compared to control arm. Analysis of anemia events was also done by treatment arm and gender. Overall, it appears that females had more anemia events reported. However, it should be noted that subjects who had lower baseline hemoglobin levels, particularly females, were more likely to receive an intervention for anemia and have that intervention earlier, and, thus, would be reported more frequently as having had an anemia event. When you look at the lower row, this is a subset of subjects with similar baseline hemoglobin. This difference is not seen.

In the Phase 3 trials, grade 3 and grade 4 neutropenia was reported more frequently in boceprevir-containing arms compared to control. Neutropenia was reported as a serious adverse event in three subjects in boceprevir-containing arms compared to none of the subjects in the control arm. Neutropenia resulted in study drug

discontinuation in eight subjects in boceprevir-containing arms compared to none in the control arm. As presented by the applicant earlier, GCSF use was allowed in the Phase 3 trials.

Three subjects, all in boceprevir-containing arms, experienced severe infections within two weeks of grade 3 and 4 neutropenia. These include a case of epiglottitis, which was life-threatening and required tracheostomy; an upper respiratory tract infection resulting in hospitalization; a case of severe salmonella gastroenteritis.

Additionally, two cases of life-threatening neutropenia, both in boceprevir-treated subjects, were reported in Phase 2 open label trials. One subject developed multi-organ system failure due to sepsis and the other experienced a fever of 104.5 degrees Fahrenheit. A specific infection was not reported in these cases.

In Phase 3 trials, as shown in the table, a higher proportion of subjects in boceprevir-containing arms than the PR arms experienced grade 3 or 4 lowest platelet count on treatment.

Thrombocytopenia was reported as a serious adverse event in three subjects in boceprevir-containing arms compared to none in PR arms. Thrombocytopenia resulted in study drug discontinuation in four subjects in boceprevir-containing arms and in none of the subjects in the PR control arms. No cases of significant bleeding were reported in Phase 3 trials. However, one of the subjects received multiple platelet transfusions because of severe thrombocytopenia.

In conclusion, the most notable safety concern is the additional decrease in hemoglobin above and beyond that observed with pegylated interferon and ribavirin therapy alone. Boceprevir-treated subjects experienced more anemia, neutropenia, and thrombocytopenia. These appear to be part of an overall bone marrow suppressive effect of boceprevir.

Anemia appeared to be managed effectively during the clinical trials and was reversible after all the study drugs were discontinued. A few serious or life-threatening infections were

reported. Close monitoring of laboratory parameters is recommended in clinical practice if drug receives marketing approval.

Now, I will briefly summarize the clinical resistance issues.

This table summarizes a pooled analysis of substitutions that emerged in boceprevir-treated subjects who failed to achieve SVR in either of the two Phase 3 trials. Slightly more than half of boceprevir treatment failures had at least one of these specific boceprevir treatment emergent substitutions detected. Patterns of treatment-emergent substitutions were different in genotype 1a and genotype 1b subjects, as shown in this table.

A relatively small proportion of study subjects had one or more of the major boceprevir treatment emergent substitutions detected as baseline polymorphism. These substitutions were detected using population-based nucleotide sequence analysis. So the viral populations carrying these substitutions are highly evident in these 40

subjects.

A pooled analysis of SVR rates from these subjects was conducted to explore the effect of having detectable baseline boceprevir resistance-associated substitutions on treatment efficacy. As shown in this table, this analysis is limited by the small number of subjects with these substitutions at baseline, but it appears that these detectable substitutions reduced boceprevir efficacy among subjects with less than 2 log decline in response to PR therapy compared to those without baseline substitutions; a possible effect on boceprevir efficacy among subjects with a relatively poor virologic response to pegylated interferon and ribavirin therapy based on lead-in period.

Certain boceprevir treatment emergent substitutions may persist at a high level for years in some patients who fail a boceprevir-based treatment regimen. Based on an analysis of long-term follow-up isolates from subjects who failed to achieve SVR in Phase 2 boceprevir trials,

approximately 25 percent of subjects with one or more boceprevir treatment emergent substitutions still had at least one such substitution detected after 2.5 years of follow-up.

The substitutions that remained detectable were mostly T54S and R155K. Note that these data are based on population nucleotide sequence analysis, which typically does not detect variants that comprise less than 25 percent of the total viral population.

Now, let's look at some of the efficacy results and issues. Some of the terms commonly used to describe treatment response in patient populations were earlier described by Dr. Birnkrant. It should be noted that applicant's non-responders include partial responders, but does not include null responders, as defined above.

I'll go over the primary efficacy results in the treatment-naive population.

This slide shows the trial design for the treatment-naive population, which has been already presented by the applicant. As you know, this

trial had three arms. Arm 1 was the control arm with pegylated interferon and ribavirin therapy for 48 weeks. Arm 3 was a triple therapy arm with pegylated interferon and ribavirin for an additional 44 weeks after four weeks of lead-in. All three arms had four weeks of lead-in therapy with PR. Arm 2 was the response-guided therapy arm, and subjects in this arm received a different duration of therapy depending on virologic response at weeks 8 through 24. I will discuss this later.

Two separate population cohorts were enrolled in the treatment-naive trial; cohort 1, non-black subjects, and cohort 2, black subjects. However, for the primary endpoint analysis, cohorts 1 and 2 were combined. Overall SVR rates were 63 to 66 percent in boceprevir-containing arms compared to 38 percent in controls. Relapse rates were lower in the boceprevir-treated subjects compared to controls.

SVR rates were lower in cohort 2, black subjects, than in cohort 1, non-black subjects, for both boceprevir treatment groups, arm 2 and arm 3.

But this was also true with the PR control arm. Within each cohort, SVR was higher in both boceprevir treatment arms than in the PR control arm. In cohort 2, black subjects, there was an 11 percent numerical difference in SVR between the RGT boceprevir arm and the 48-week triple therapy boceprevir arm. This is of some concern and could be of clinical significance.

Now, I will walk you through the response-guided therapy arm in the treatment-naive trial. As I said earlier, all subjects received four weeks of lead-in therapy with pegylated interferon and ribavirin, which is also referred to as standard of care therapy.

All subjects received 24 weeks of boceprevir in combination with PR after the first four weeks of lead-in period. For subjects with undetectable HCV RNA at treatment week 8 through treatment week 24, all three drugs were stopped at week 28, and these are also referred to as early responders.

While those with detectable HCV RNA at week 8, but undetectable at week 24, boceprevir was

stopped and subjects received an additional 20 weeks of PR therapy. These subjects are also referred to as late responders. For subjects in each of the treatment arms, all treatment was discontinued for futility if HCV RNA was detectable at week 24.

This analysis shows the comparison of early responders in the RGT arm to those subjects in arm 3 who had a similar virological response. Early responders were compared to the subjects in arm 3 who were HCV RNA undetectable at treatment week 8 up to treatment week 24 and received treatment duration greater than 31 weeks. SVR was similar in both arms, in the RGT arm, as well as triple therapy arm 3, 97 percent versus 96 percent.

In late responders, subjects in the RGT arm who were assigned to longer therapy were compared to subjects in arm 3 who had HCV RNA detectable at treatment week 8 or at any subsequent visit up to treatment week 24.

SVR was numerically higher, approximately 9 percent, in the triple therapy arm 3, than the

RGT arm 2 and these late responder subjects. This difference was not statistically significant, but the trial was not designed to detect differences in this subgroup.

Our analysis differs from that presented by the applicant, and then I will explain it in the next slide. Arm 2 was the RGT arm. Subjects who were undetectable from treatment week 8 through treatment week 24 are referred to as early responders. However, subjects who were detectable at treatment week 8, but undetectable at treatment week 24 are referred to as late responders.

There were 14 subjects who should have received 28 weeks of treatment duration, HCV RNA undetectable through treatment week 8 through treatment week 24, but received longer duration of therapy and, hence, were excluded from the FDA analysis.

These 14 subjects in arm 2 were really early responders but received the wrong duration of therapy because of detectable HCV RNA results that were not confirmed with a second analysis. One

subject should have received 48 weeks of treatment based on HCV RNA detectable at treatment week 24, but received a shorter duration of therapy of 28 weeks treatment. Hence, this subject was also excluded from our analysis.

There were some subjects classified as other who discontinued treatment prior to week 28 assignment due to reasons for treatment failure or discontinuations due to adverse events, and these are not included in the analysis, as well.

On the right side of the slide you will see the triple therapy arm, which is boceprevir and PR for 44 weeks after lead-in therapy. And the subjects who received more than 31 weeks of treatment and who had any positive from treatment week 8 through treatment week 24 were compared with late responders in the RGT arm. So the subjects -- the early responders in the RGT arm were compared with the similar responders in arm 3, and those late responders in the RGT arm were compared with the similar responders in arm 3.

So just to reiterate, this 9 percent

difference between RGT arm and arm 3 and late responders, cohort 1 is very similar to overall. Cohort 2 is similar, although the differences are bigger. But you should note that these numbers are very small, and this is not statistically significant.

Now, I'll discuss efficacy results in the treatment-experienced trial. This is a trial designed for the treatment-experienced trial, and, as you may recall, arm 1 and arm 3 are similar to the treatment naive trial. The only difference here is in the RGT arm, which is the response-guided therapy arm.

Subjects received different treatment durations depending on virologic response at weeks 8 and 12, and I will discuss that later. In all treatment arms, subjects with detectable HCV RNA at week 12 discontinued all therapy for futility and were considered treatment failures.

This slide shows the primary efficacy results for treatment-experienced population. SVR was higher and relapse rates were lower in both

boceprevir-containing arms compared to the PR control arm. However, SVR was numerically 7 percent higher in arm 3 than in the RGT arm in this population. The 7 percent difference in SVR between the two arms was due to differences observed by subjects in each arm who were receiving identical therapy prior to week 36, and this may be due to the differences in responses in the subgroup of subjects with cirrhosis, as pointed out by applicant earlier. Within the boceprevir treatment arms, subjects who were previous relapsers had higher response rates than those who were previous partial responders.

This slide shows you the response-guided therapy for the treatment-experienced trial. All subjects received four weeks of standard of care therapy, followed by eight weeks of boceprevir and standard of care therapy.

Virologic response was checked at treatment week 8 and treatment week 12. Subjects with an undetectable HCV RNA at week 8 completed all therapy at week 36, and these are referred to as

early responders, while those with detectable HCV RNA at week 8, but undetectable HCV RNA at week 12 received triple therapy through week 36, followed by an additional 12 weeks of PR alone. These are referred to as late responders.

In all treatment arms, subjects with detectable HVC RNA at week 12 discontinued all therapy for futility and were considered treatment failures.

This slide shows you the response rates compared for early responders and late responders in arm 2 versus arm 3. Early responders had higher response rates of greater than 90 percent in both boceprevir-containing arms. Response rates were also similar in late responders in the RGT and triple therapy arms.

Primary efficacy results for advanced fibrosis are patients with cirrhosis at baseline that are presented in this table here. In the treatment-naive trial, subjects both had higher METAVIR fibrosis scores or cirrhosis had lower SVR than those with lower scores or no cirrhosis at

baseline.

Patients with cirrhosis or advanced fibrosis did better with longer triple therapy arm than shorter response-guided therapy arm. This was seen in both treatment-naive and treatment-experienced subjects. We think the difference in SVR between RGT and the longer triple therapy arm is mainly driven by those with cirrhosis.

To conclude, overall, in the treatment-naive subjects, SVR was 63 to 66 percent in boceprevir-containing arms compared to 38 percent in the control arm. Overall, in the treatment failure subjects, SVR was 59 percent to 66 percent in boceprevir-containing arms versus 21 percent in the control arm.

The treatment difference was substantially significant and robust for each trial based on the primary efficacy endpoint. Relapse rates were also lower in boceprevir-treated subjects. Efficacy of boceprevir was demonstrative in subjects regardless of race. Response-guided therapy approach in early responders provides a potential shorter duration of

therapy.

This concludes my portion of the presentation, and Dr. Florian will continue over the next part of the presentation.

FDA Presentation – Jeffrey Florian

DR. FLORIAN: Thank you, Dr. Mishra.

For my part of this presentation, I am going to cover two key questions. The first question relates to the evidence of effectiveness for prior null responders.

The applicant provided us information in treatment-experienced subjects who were prior relapsers and prior partial responders. However, the applicant did not explicitly study the prior null responder population. So question 3 to the committee is to weigh on the evidence for use of boceprevir in combination with PR in prior null responders.

So let me walk you through the rationale to illustrate that the treatment-naive population can inform about drug effect in null responders. Shown here on the left in the pie chart are treatment

outcomes on PR from treatment-naive P05216. The distribution of end-of-study response rates are expected based on our experience with PR treatment.

What we have learned in this review is that week 4 decline is an indicator of end-of-study responses. As expected and shown on the right are week 4 viral log declines grouped according to their response. As expected, the responders had the highest decline by week 4, shown at the top, and null responders had the lowest, at the bottom.

If we select a less than 1 log decline at week 4 to identify null responders, a large portion of the subset will also include subjects who may have been partial responders, relapsers, or responders. Alternatively, we can select the population comprised predominantly of null responders using a less than 0.5 log decline.

Now, because the lead-in with PR was included in both the control and boceprevir arms, we can look at the week 4 response in the boceprevir treatment arms and derive information on drug effect in prior null responders.

First, let's focus on the PR-treated subjects who had a less than 1 log decline at week 4, and we see that 69 percent of these subjects were null responders and that 4 percent of the subjects in the PR group achieved SVR.

For boceprevir-treated subjects with a week 4 response during PR lead-in, less than 1 log, we see that the SVR in these subjects was 28 percent in the RGT arm and 38 percent in subjects treated with boceprevir for 44 weeks. This analysis shows an improvement in SVR with the addition of boceprevir, but may overestimate SVR as this analysis includes a proportion of subjects who are not null responders.

If we perform the same comparison for less than 0.5 log decline at week 4, we see that 88 percent of these subjects, or 22 out of 25, were null responders. SVR for subjects treated with PR in this group was 0 percent, while subjects receiving boceprevir who had PR lead-in response less than 0.5 had an SVR of 28 to 30 percent.

Again, an improvement over PR was observed

with the addition of boceprevir, but a less than 0.5 week 4 response selects a population that is primarily null responders and provides a more conservative estimate of SVR in this population.

Summarizing these observations, data from subjects with less than 0.5 or less than 1 log decline at week 4 provides information about boceprevir's effectiveness in prior null responders. Also, treatment with boceprevir improves SVR in these subjects compared to treatment with PR.

Now, it is anticipated that these subjects would be the most difficult to treat and as such, they may benefit from a full 44 weeks of boceprevir treatment regardless of initial response.

So returning to the original table for treatment-experienced subjects, one option, one possible option for prior null responders would be what is shown on the far left, four-week PR lead-in, followed by 44 weeks of boceprevir plus PR.

I'd now like to discuss the second question that relates to treatment duration in treatment-

naive subjects. For this question, we would like you to weigh in on treatment duration for the treatment-naive late responders, as we believe this population may require a longer duration of boceprevir and was originally studied and proposed by the sponsor.

Shown here are the SVR results for the boceprevir treatment arms from P05216, according to the FDA analysis discussed earlier, for early and late responders. As has been presented previously, there was no difference in SVR between early responders receiving treatment for 28 weeks or 48 weeks. However, shown at the bottom of this table, a 9 percent numerically lower SVR rate was observed for late responders in the RGT arm compared to subjects receiving boceprevir for 44 weeks. Based on this observation, we explored what was happening in these late responders once boceprevir treatment was stopped.

The plots here show percent of treatment-naive subjects with undetectable viral load on the Y-axis at each visit over the course of the trial

on the X-axis. On the left-hand side, we have treatment-naive early responders, and we see that both early responder treatment arms had similar results, responses, further supporting the selection of 28 weeks of treatment in treatment-naive early responders.

In contrast, on the left side, which is treatment-naive late responders, the percent of subjects with undetectable viral load separates immediately after removal of boceprevir in the RGT arm at week 28 due to viral breakthrough during treatment with PR. This demonstrates that 24 weeks of boceprevir treatment may be suboptimal in treatment-naive late responders.

Based on this observation, one treatment option for treatment-naive late responders would be four weeks PR lead-in followed by 44 weeks of boceprevir with PR, and the evidence for this regimen was from the treatment-naive late responder treatment arms where this arm performed better for the RGT in late responders.

What I'm going to show next is that we may

have another treatment option to consider by bridging data from the treatment-experienced patients. Before I introduce the information on bridging, let me walk you through the concept that we have learned during this review to help us with this decision.

Now, when a treatment-naive subject is first treated with PR, these subjects may have one of four treatment outcomes: responder, relapse, partial response, null responders. Those subjects who don't achieve a response would be considered the treatment-experienced subjects.

Now, when these subjects would be re-treated with PR, what do we expect their response to be and how does this tie into a patient's response when they were first treated with PR?

Design of these studies has allowed us to make comparison between the treatment-naive subjects from P05216 receiving PR and treatment-experienced subjects from P05101, whose prior PR outcome is already known using their week 4 response. The week 4 response data has also

allowed us to extend these observations to early and late responder subjects from the boceprevir treatment arms as all treatments included four-week PR lead-in.

For the first point, it was observed that the week 4 response was similar between treatment-naive subjects treated with PR who relapsed during treatment, shown as the first line in this table, and the treatment-experienced subjects who were prior relapsers. We see the mean response was similar between these two groups.

Likewise, week 4 response was similar between PR treatment in treatment-naive subjects who had a partial response, shown as the third line in blue, and treatment-experienced subjects who were partial responders, shown as the final line.

Now, only the median values are shown here, but the intra-quartile ranges were also similar for these groups. This observation tells us that the week 4 responses is similar in subjects whether receiving PR for the first time or having received it previously.

For the second point, let's look at the week 4 responses in treatment-naive subjects treated with PR who failed treatment, shown as the top three lines, going as relapsers, partial responders, or null responders. If we then look at the week 4 responses for the late responders from either the treatment-naive or treatment-experienced studies, we observe that these subjects have similar week 4 responses to those subjects who went on to fail PR treatment.

So what we've seen is evidence that the PR response is similar for subjects receiving PR treatment for the first or subsequent times and that the late responders are those subjects who may have failed treatment with PR alone. Together, these observations allow us to make a comparison between late responders in the treatment-naive and treatment-experienced trials.

The plots here, again, show percent of subjects with undetectable viral load along the Y-axis at each visit over the course of the trial along the X-axis. Now, on the far right we have

the figure for the treatment-naive late responders again, and on the far left, treatment-experienced late responders.

What we see is that the late responders in the treatment-experienced trial, which only enrolled prior relapsers and prior partial responders, had similar trends for both boceprevir arms. No separation between the treatment arms was observed once boceprevir was stopped at week 36.

Also, at the bottom, we observed SVR for late responders from this trial were similar for both arms. It supports 32 weeks of boceprevir in the treatment-experienced late responder population, where null patients were excluded and could be applied to treatment-naive late responders.

So going back to the tables we have shown, based on these observations and presented as option 2, one treatment option would be four weeks of PR, followed by 32 weeks of boceprevir plus PR, followed by 12 weeks of PR. And the evidence for this treatment regimen would come from the

treatment-experienced trial and the bridging analysis that we've shown on the previous slides.

So bringing everything together for the treatment-naive and treatment-experienced patients, treatment options for these patients may look as follows.

Under the treatment-naive late responder group, both options are presented and will be reduced to one based on feedback from the committee.

Now, it should be noted that both of the currently proposed treatment options may result in suboptimal treatment duration in a subset of patients based on the currently proposed set of treatment-experienced regimens. What we mean by this is that treatment-naive late responders that are similar to the prior partial responders and prior relapsers may receive unnecessary additional boceprevir treatment if the first option, the PR4, 44 weeks boceprevir plus PR, is used.

Likewise, treatment-naive late responders, similar to prior null responders, may receive a

suboptimal treatment duration with treatment option two. However, more granularity in the late responder treatment may overcomplicate treatment for these patients without substantially contributing to subject benefit-risk ratio.

Clarifying Questions from Committee to FDA

DR. CARGILL: Clarifying questions from the committee for the FDA? And then we will proceed.

Ms. Dee?

MS. DEE: I'm wondering, on the safety, our briefing document talks about the open label use of EPO and the AE reporting system that was used by the sponsor. And it says that interventions actually led to AE reporting and that 21 percent of patients that actually had a less than or equal to 10 GDO decrease were not reported as adverse events and that the discretion of the investigator actually led to -- using the discretion of the investigator instead of hard and fast rules led to differences in reporting and inherent miscalculations and claims that it makes this analysis limited and that only simple

characterizations are possible.

I didn't hear that in the FDA presentation.

Is that still the agency's position? I'm trying to understand if, in fact, these data are reliable when it comes to the number of cases of anemia.

DR. COOPER: Those issues mainly affected our ability to interpret subgroup analyses, because there were differences across treatment arms within the subgroups with regard to whether interventions occurred and according to baseline hemoglobin.

So the main issue was with regard to confounding you to baseline hemoglobin and differences in interventions impacted our ability to interpret subgroup analyses. So that was the main limitation incurred by those findings.

MR. TRAN: Could you state your name into the record, please?

DR. COOPER: Chuck Cooper from FDA.

MS. DEE: So in other words, can we expect more cases of anemia and more serious cases of anemia if people aren't allowed to use EPO for

whatever reason, if this is approved?

DR. COOPER: I'm not sure we can answer that question from this data. There was no formal comparison made with regard to patients who received ESA versus those who didn't receive ESA as part of the study design.

MS. DEE: So are the data confounded and biased because of this EPO use and this discretion of the investigators instead of hard and fast rules? Help me understand that.

DR. COOPER: I think when you're looking overall at what happened, I think you can believe that what happened to the patients is accurately represented according to the interventions that actually occurred. But I think when you start to look at subgroups, such as by race or gender or sex or other subgroup analyses, then these confounders actually -- as you saw with the example of females versus males -- can actually have a significant impact on your ability to interpret the results of the subgroup.

So that was the main point there, that

differences in interventions and differences in baseline that exist between each treatment group, within whatever subgroup you're looking at, can have an impact and make the ultimate subgroup analyses difficult to interpret and potentially misleading.

So it really has to do with subgroup analyses, and that's the reason why we actually didn't present any subgroup analysis, because we didn't have the time to try and do corrections for these different issues. But we fully intend, after we have more time, to explore subgroup analyses, trying to control for these different things.

MS. DEE: Okay. And one more quick question.

The data in blacks, what I read when I read the briefing paper was that the agency didn't seem to be confident that response-guided therapy versus 44 weeks of boceprevir and PR was -- in other words, response-guided therapy wasn't sufficient, and that's not what I heard today.

So what's the issue there?

DR. MISHRA: So further analyses were done, and, at this point, we think that most of those differences in the responses are driven by subjects with cirrhosis. Applicant has presented that data, and we have confirmed with our own analysis, and we do believe that those differences are mainly driven by subjects with cirrhosis.

MS. DEE: And the numbers of blacks and people with cirrhosis were enough to make you feel confident that that's correct.

DR. MISHRA: We have to keep in mind that these subset numbers are very small.

DR. CARGILL: Dr. Strader?

DR. STRADER: I have two questions, but first I want to follow-up on the question that she just asked.

Are you saying that there are sufficient number of black patients in the study with cirrhosis that we can say that we would recommend a method of treatment for them?

DR. MISHRA: No. I'm not saying that the numbers are sufficient. They are small numbers,

but still we have seen the patients with cirrhosis or in advanced fibrosis stage at 4. Those with triple therapy did better than response-guided therapy. So our recommendations at this time are that maybe subjects with cirrhosis at baseline should be treated with triple therapy, boceprevir, for 44 weeks.

DR. STRADER: Including black patients with cirrhosis is what I'm asking.

DR. MISHRA: Yes. Yes. All patients with cirrhosis.

DR. STRADER: Okay. And my original question, I'm confused a little bit about the explanation for why null responders should be treated. It appears in the briefing document, in the beginning, they were excluded from the trial because there was insufficient data in the Phase 2 trials to suggest that these patients might respond.

Now you're saying that based on what happens in the group of naive patients, that there is going to be a subset of people who would be null

responders; that somehow we should extrapolate that data from the group of naive patients into the group of mull responders.

There appears to be a difference between people who relapse and people who have partial response to all three drugs. So I'm not quite sure why you think that that doesn't extrapolate to null responders. Someone who did not respond to a prior course of interferon and ribavirin would not be different than someone who had a partial response or a relapse.

DR. MISHRA: I will have our pharmacometrics team to answer that question.

DR. FLORIAN: So if I understand the question, it's not so much is this working in the group, but is it asking why the recommendation is at 44 instead of 32?

DR. STRADER: No. It's asking why you're saying --

DR. FLORIAN: It's asking why a recommendation --

DR. STRADER: -- null responders. They were

specifically excluded, but you're trying to give us a justification for why they can be treated now, and I'm trying to understand your justification for that.

DR. FLORIAN: You're correct that they were originally excluded, but during the course of analysis, looking at that treatment-naive group, we believe that we can use information from that population to show -- select a subset of patients who if, instead of receiving boceprevir with PR, if they had received just PR, would have resulted in a null response, and then perform that comparison between what those response rates -- just get an idea on what an SVR rate might be in this population had it actually been studied.

DR. STRADER: So you don't believe that a prior null responder, someone who did not respond to pegylated interferon and ribavirin in the very beginning, is different than a prior relapser or a prior partial responder is what you're saying.

DR. FLORIAN: No. We are saying they're different.

DR. STRADER: In what way? You're saying you can use data from people who have not been treated and compare the two.

DR. FLORIAN: So in the prior -- when you're looking at the treatment of experienced, we are saying they should be treated different, those two groups.

DR. JADHAV: Pravin Jadhav, team leader, pharmacometrics. Let me offer more help here.

I think the question you're asking is, are prior relapsers and partial responders, do we think they're different. And there are data to show that the applicant's analysis, as well as our analysis, has shown that SVR in that combined population is about 66 percent.

What we have done is to get us an idea about what's that drug effect in null responders, we looked at less than 1.0 log or .5 log, and that treatment effect turns out to be 30 percent.

So these analyses show that the response to these triple therapies in null responders compared to the partial responders and relapsers is lower.

The second question you were asking at the beginning was we didn't exclusively study the treatment-experienced trial, for sure, but, again, as Dr. Florian mentioned in his presentation, we have learned during this review that even naive populations can inform us about the drug effect in the experienced. It's unlike HIV, where your response, after you fail the fourth round, changes because of mutation. That's a very distinct difference we had to make here in HCV. After the fourth round of therapy, your response to peg/ribavirin on which you fail is still the same.

So the patient process still remains the same, except in the second part, we know who they are. But week 4, where it comes in is it tells us about interferon responsiveness. And we can choose who are those -- as Dr. Florian mentioned in his presentation, who are those future null responders, and because you believe the future null responders and the prior are the same, we are able to link and get an estimate of drug effect that may not be accurate, but what this data shows is better than

just treating them with peg/ribavirin.

Is that clear?

DR. STRADER: No, but --

[Laughter.]

DR. JADHAV: All right. I tried.

DR. VAN DYKE: Can I just follow-up on that? Because you pretty much had sold me when you presented the slides, but now I'm thinking more.

It seems to me that the non-responders who have already non-responded are different than the presume non-responders that haven't failed yet, but you're thinking they will. So it's kind of hard to compare them directly, because you don't know the response of the non-responders who haven't been treated yet, the future non-responders. It seems to me that they're likely to be different than the non-responders who have really non-responded.

DR. JADHAV: Can I have slide number 69 from our backup slides, 69?

So what is shown here is the treatment outcome in the pegylated interferon/ribavirin arm for relapsers after they ended their study; so knew

this end-of-treatment status and we looked back at what happened at week 4.

So at week 4, we didn't know who these patients were going to be, but we went and looked at their end-of-treatment status, and we found there were relapsers and partial responders and plotted out the box plots for their week 4 response.

Next. On the other hand, in the treatment-experienced trial, we knew who they were. At the beginning it says they were the prior relapsers and the partial responders.

If you look at the distribution of responses, whether they were future, that is the left side, or the known, it is still the same. That's why these are the same patient population to which, on an average, the treatment PR responsiveness -- to be very clear, the PR responsiveness hasn't changed.

So it is not on this slide, but if I bring in the third one, which is the null responder, which will be the lower end of this curve, whether

it's the first round or the second round, they will still be the same. That's why we think the first round of treatment in these patients can inform us what will happen to the drug effect on the second round, because we have the data from treatment-naive population who were the null responders at the end of the study.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Thank you. Maybe if I could just continue on this and then I'll get to my original question.

So what you're trying to tell us is that a week 4 response is essentially the same as a week 12 response in terms of that the week 4 antiviral decline is predictive of the week 12.

But what about development of virological breakthrough and resistance in those patients? Because, one, you're dealing with a treatment-naive group and the other with an experienced group. So I don't think there's data to answer that question.

Is that correct?

DR. JADHAV: We are not saying that week 4

response is predictive of week 12. And, in fact, the resistance doesn't come into this argument, because we're only talking about the PR responsiveness to link these patients.

DR. GHANY: Yes. But you're saying that a week 4 peg/ribavirin response equates a week 12 null response.

DR. JADHAV: Yes.

DR. GHANY: Isn't that what you're saying? That's the argument that you're trying to make.

DR. JADHAV: Specifically, if you talk about null response, because it's defined at week 12, yes. What I meant was week 4 response is informing us about what will happen at the end of the study. Well, for null responders, the end of the study is week 12, because they are done there.

But what I'm saying is you can grade them -- Dr. Florian has one of the slides where he showed greater week 4 response for the responders being the highest and the null responders being the lowest. It's telling us what will happen to them at the end of the study. Week 4 itself, you can

kind of tell what will happen. That's what I mean.

DR. GHANY: So I understand that. But then my question is, do we know about the development of virological breakthrough in these patients during therapy?

So my question is, would a null responder have a higher rate of virological breakthrough than a naive patient who fails to achieve a week 4 interferon response?

DR. MURRAY: Well, we think that that has been studied in the naive population, the people who had -- if you pick less than a half a log, 80 percent of those people would be null responders if just given peg-interferon. And those people, when they added boceprevir in the naive trial after four weeks, still had an SVR rate of 30 percent, around about.

Now, do we know exact magnitude of a null responder? No, because they weren't studied. But I guess what we're saying -- that this is a question for the committee to decide. We're just offering some evidence that might give you some

flexibility to consider whether to include them or not. But what we're saying is, is it likely that boceprevir offers an added benefit, and we are saying, yes, by the data in treatment-naive , it's almost inconceivable that they wouldn't have a benefit of boceprevir.

When you look at the four-week response, if it's less than half a log, about 80 percent, 90 percent of those would be null responders. And in the ninth trial, they did add boceprevir, and they still had some sort of response, which was zero, and in the PR arm, about 30 percent. It's a pretty big number treatment difference to be able to explain away as having no effect at all in that population, who would be null responders. But we don't know exactly what it is.

Are they exactly the same? No. Four-week would be a surrogate for 12-week.

DR. CARGILL: Dr. McGovern?

DR. MCGOVERN: The sponsor said that the reason that they did not study the null responders was because they were concerned about essential

monotherapy. I'd like to follow-up on Dr. Ghany's question in that I would like to know -- I don't think there's a question that the addition of boceprevir changes virtually a null response to about a third of those patients getting a response.

I think what I'd like to know more about are the people who don't get the SVR. Do we have any information about teasing out virologic resistance based on the four-week virologic response to peg/riba of less than a log? Are the numbers of RAVs enriched in patients who have less than a 1 log drop? That would be helpful to know. In term so a risk of exposing null responders who have not been studied in this trial, that would be very helpful.

DR. MISHRA: I'll have Dr. Patrick Harrington from our virology team to answer that question.

DR. HARRINGTON: Yes. The relationship between interferon responsiveness and the ultimate detection of resistance variance upon treatment failure is quite clear. Those who respond more

poorly to the peg-interferon/ribavirin lead-in phase are more likely to have the detection of resistance-associated substitutions upon treatment failure compared to those who respond more favorably during the lead-in phase.

So it's about 70 percent of patients who have a less than 1 log decline at week 4 who then go on and fail to achieve SVR have a detectable resistance-associated variant at the end of treatment compared to somewhere about 35 percent of those who fail treatment but have a greater response during that lead-in period.

DR. MCGOVERN: Just a follow-up, too. In terms of this issue of using week 4 as predictive of what happens at week 12, there were documents that were given to us by the sponsor that had a table that I felt, when I looked at the table, that if you had more than a 1 log drop, that issue of predicting more than a 2 log drop at week 12 was much tighter than if you had less than a 1 log drop as to whether you would have less than a 2 log drop at week 12.

So I guess I'm still wondering. Are we really truly convinced that what happens at week 4 defines a null responder? And we've looked at this for years before this. This isn't the first time this has come up.

DR. FLORIAN: Just on that point, with the 1 log drop, that was sort of the motivation on why we looked at an even lower decline. It was recognizing that the 1 log drop, there were other patients within that group, except for null responders. When you go down to like a half a log drop, what we saw is that you were getting closer and closer to a homogenous patient set that are null responders.

Certainly, I think one thing that might be asked, if the data is available from IDEAL trial, putting together that similar table, but for a half a log, and possibly after lunch, that's something that could be looked at.

DR. CARGILL: Dr. Knodell?

DR. KNODELL: Knodell. These resistant mutants are what are responsible for most people

not responding and getting an SVR -- perhaps this should go to the sponsor. But how long a time period was needed before you could access or admit a non-responding patient to this trial? And has anybody looked at whether the duration between prior treatment and access to this trial or admission to this trial had anything to do on these early viral responses, whether that time period is -- because we know these mutants last or are around for a long time. And if there is a difference in time period between a previous treatment and accession into one of the boceprevir trials, that may well affect your early virological response.

What was the interval that was required between treatment, prior treatment, and accession into one of these trials?

DR. SINGER: I think we'd ask the sponsor to answer that question.

DR. ALBRECHT: For the treatment-experienced trial, a patient must have finished his last course of peg/ribavirin at least six months. However,

there were patients that were in the trial that had been off drug for several years, because, as you'll remember, these are people that were treated and for reasons, probably because they knew they wouldn't re-respond, they weren't re-treated again.

DR. KNODELL: Do you know whether there was any difference in virological response as to whether these people had been previously treated six months ago or three years ago when the mutants would probably have disappeared?

DR. ALBRECHT: Well, basically, with peg-interferon and ribavirin, we do not see resistance. So these are patients that only receive pegylated interferon and ribavirin, so they really would not have had RAVs when they came into our trial.

DR. CARGILL: Dr. Clay?

DR. CLAY: Sorry, I'm not going to ask about the non-responder thing.

Was there any sort of analysis done looking at the timing with respect to the onset of anemia, the onset of thrombocytopenia or neutropenia? I guess what I'm thinking is, was there anything in

the way in which it presented that would give the impression of a cascade of events occurring?

DR. MISHRA: As I presented earlier, there was an initial decline during the first four weeks of therapy, which we contribute to ribavirin. And then after boceprevir was added at treatment week 4, you see an additional decline in hemoglobin which was approximately 1 gram, but which was higher in some subjects and lower in some subjects based on their baseline hemoglobin. But we haven't looked at neutropenia or thrombocytopenia as far as timing of onset of events.

DR. CLAY: And I apologize because I don't have it all memorized.

Would they discontinue or stop therapy or treat the anemia? I mean, was the potential there for someone to continue with the drop in hemoglobin that could have then gone on to develop either thrombocytopenia or neutropenia?

DR. MISHRA: I don't think I understand the question. Can you please state it again?

DR. CLAY: I'll try. Okay. In the

individuals who either had thrombocytopenia or neutropenia, did any of them have anemia or not defined in as anemia in the study, but a drop in hemoglobin prior to that occurring?

DR. MISHRA: Overall, they think that this is an overall bone marrow suppressive effect. So subjects who had anemia also had neutropenia and thrombocytopenia, but thrombocytopenia and neutropenia were to a lesser extent compared to anemia. But it seems that this was an overall bone marrow suppressive effect.

DR. SINGER: And maybe the sponsor could address that question a little further as far as timing of neutropenia and thrombocytopenia. There were some patients that were pancytopenic in the trials.

DR. KORN: Scott Korn, K-o-r-n.

Slide 103, please, from the core deck. We think this may help. We showed this earlier.

You can see that the predominant amount of the decline in the neutrophil count occurs very early within the first four weeks when there's no

boceprevir on board, and then there's a small incremental increase. This really mirrors the pattern that we saw in the anemia slide, with the decrease in hemoglobin at the same time.

So we agree with the FDA. These are occurring concurrently and not really sequentially, if that answers your question.

DR. CLAY: But it's still not broken down by individual patient, in other words. That's trends over the entire study, correct?

DR. KORN: That's correct.

DR. CLAY: Okay. Thank you.

DR. CARGILL: Dr. Ellenberg?

DR. ELLENBERG: Could you put up the FDA's slide 52, again, on the treatment-naive late responders?

So I'm a little confused by this slide. I'm looking at the bottom, and it looks like there's sort of a small number in each group, and there's 27 out of 34 versus 29 out of 40. And you're pointing at week 24 or week 28 in one place and week 36 in another.

I'm just trying to understand how much we should really believe that this little separation over there to the right is something real or whether this is easily -- could easily just be random noise. I just want to make sure I'm not -- because I was surprised at the attention to that, and I want to make sure I'm not missing something about why you think that's real. It might be real, but it looks to me like it could also just be noise.

DR. MURRAY: You're right. There are differences, small differences if you look at certain subgroups, and sometimes the differences go one way or the other in favor of either the triple or the RGT.

But I guess when we compared arm 2 to arm 3, it did seem like that there was a pattern, blacks, treatment-experienced, late responders, if your HCV RNA at four weeks was less than a log. There seemed to be a pattern for the poor responders from the outset to be doing a little worse on arm 2. So we were particularly looking for breakthroughs that

would occur after boceprevir stopped. It looked like that there might be a small difference in the naive.

Whether any of this is real, I guess that's the question that the committee is going to have to deal with. As I said, there are so many different factors that impact SVR, and we're looking at so many subgroups, but what we're trying to figure out is, I guess, maximizing SVR and decreasing toxicity. So you're right.

Then the table at the bottom goes with the figure at the left, and so that's the treatment-experienced, and a subset of those, the late responders who had received therapy for a certain amount of time, as well.

But it did seem to be -- the treatment-naive, there did seem to be a slightly different pattern than the experienced based on small numbers. It's difficult. I don't know what to tell you.

DR. ELLENBERG: They come apart and they go together, and it's --

DR. MURRAY: Well, they really don't go together on the naive. I think the difference that you see between the blue and the red lines occurs sometime right after the boceprevir is stopped at 28 weeks. And then they look like they're coming together, but really that's end of therapy. And then when you stop therapy week 4, they both declined kind of in a parallel fashion. The difference narrows a bit.

DR. HARRINGTON: I just want to add on to Dr. Murray's explanation a little bit further. If you look at the data for the patients in the right panel -- and we just use a strict definition of virologic breakthrough -- after week 28, there are 12 subjects in the RGT arm who experience a strict definition of virologic breakthrough compared to two subjects in the triple therapy arm.

So that difference between the red and the blue lines does appear to be associated with bona fide virologic breakthrough after you take boceprevir away from that regimen.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: This may just require yes and no answers. So what I'm hearing is the agency is not recommending that null responders be included. You're asking us that question; correct?

DR. MURRAY: That's correct. That's a question to the committee. We were just trying to present an argument that you might want to consider, and we're permissive to some flexibility, if you think it's sound.

MS. DEE: So in other words, it's up to us -- or not up to us, it's up to you ultimately, but it's a question for us.

So in the lead-in, the four-week lead-in predicts outcome, ultimate SVR outcome, but that doesn't mean -- it doesn't say anything about null responders, per se, really about their SVR outcome as far as these trials are concerned.

DR. MURRAY: Lynda, state the last part of your question again, please.

MS. DEE: So in other words, we've got null responders in this naive trial. We know they're in

there, okay? And we know that some people that do worse during the four-week lead-in period will probably -- may be nonresponsive.

Does that mean that we know that boceprevir and PR for 44 weeks plus the lead-in is going to be sufficient for those patients?

DR. MURRAY: Well, that's the longest duration that was studied in arm 3. I think that's the length that I had problems with, is that the null responders -- duration of null responders was not really studied. So if you look at a half log and use that as a cutoff for null responders, most null responders had greater than a half log. The median was greater than a half log.

So I think when we use a half log cutoff, it's kind of the worst case scenario. Those are the worst of the worst of the null responders, and it looked like they would still have a treatment effect when you added boceprevir.

How long do you treat them? That's up in the air. So I think the default for us was the maximum amount that was studied as far as the

safety database, and that would be a 44-week after the four-week lead-in.

Could you go shorter? Maybe, but I wouldn't know how to really tease that out.

MS. DEE: Right. And what we've also heard is people that are null responders that don't have SVR will definitely have boceprevir resistance, resistant mutants. They're detectable in these patients, correct?

DR. MURRAY: Again, if the null responders -- again, rephrase your question.

MS. DEE: So in other words -- I can read it to you from here. In other words, these people that don't respond will have resistance, boceprevir resistance at failure, detectable mutants at failure. Right?

DR. MURRAY: I think the answer would be most. But, Patrick?

DR. HARRINGTON: For somebody who is poorly responsive to peginterferon and ribavirin, based on the lead-in phase, you can assume that the majority of treatment failures will have a treatment

emergent resistance-associated substitution.

MS. DEE: Right. So the danger is resistance for these patients rather than an SVR, correct?

DR. HARRINGTON: Right. Right.

MS. DEE: And this might be for the sponsor, but on slides 61 and 62, they talk about -- they showed this difference in the null responding patients. And I'm wondering. It looks like to me that there are less than 40 patients in the RESPOND and SPRINT studies.

Do you think that's relevant at all?

It's actually the sponsor's slide.

DR. GOTTESDIENER: Would you like us to respond to that question?

DR. CARGILL: Yes, please.

DR. GOTTESDIENER: So before we get into this particular question, maybe I could help just clarify one or two points that have come up that really seem to be causing a lot of confusion for the group as a whole.

The sponsor has actually put forward three

arguments why we think, in fact, we can understand what the treatment regimen and the effect of boceprevir would be for null responders, one of which we obviously share with the FDA. The second one is the question that was being addressed today, and the third one is even some additional data, as well.

Let me start with the question that was just asked, and if the chairman will allow me just one or two more minutes, I'll see if I can get back to the FDA question and see if I can just help to clarify that a little bit, because it's hard to listen to some of this. We know now complex it is for people who have been thinking about this for some period of time.

If I could show the PROVIDE data from the main presentation. If you could put up slide 63, please.

So this will address the final question. This is data that is unequivocal data from historic null responders. So in this particular population, you don't have to believe anything about treatment

week 4, who is poorly interferon responsive, don't really have to make any assumptions at all.

These were people who were in the boceprevir trials, Phase 3 trials, who were in the control arms failed and who were null responders by meeting the definition at treatment week 12, less than 2 logs definition. And if we rolled this people over into a boceprevir trial, where they receive 44 weeks of boceprevir in that particular trial, what you can see is -- and we don't have SVR data yet, but what you can see is these people haven't quite gotten to SVR yet. They will be in about 12 weeks.

But what you can see is there are 38 of those patients who were in that trial who have received a boceprevir regimen for 44 weeks on top of the lead-in, and in that population, 39 percent of them have achieved end-of-therapy undetectable values.

Now, there are two ways to take a look at that data. One can say to themselves, "Well, this compares very favorably in the poorly interferon responsive patients who were actually in the trial

where the end of therapy data was 44 percent."

The other way one can look at that and try to estimate what the SVR rates are going to be is by applying the relapse rates from the previous trials, and those relapse rates were about 10 to 15 percent. So if one takes 10 to 15 percent of the 39 percent, the final SVR rates are very strongly predicted to be somewhere around 30 to 35 percent.

So this data, historical null patients, really supports that boceprevir can have a 30 to 40 percent effect overall.

Now, we find this data reassuring if we don't have SVR data because it agrees with the same conclusions that the FDA and we do if we look at these patients a different way.

I think what the FDA has been saying, and we strongly endorse this, is that the definition of poorly interferon responsive, null responders, the less than 2 logs at treatment, is just one definition to define these patients. It's a very useful definition.

What we've done is we've said, if you take

an alternate definition of these patients, which is very easy to assess in our trials, because, remember, we did a four-week lead-in in all of our trials, so that data is available to everybody.

Let's see how we do.

DR. CARGILL: Excuse me. I'm going to say that I think that will help us right here, so we can keep moving our questions forward.

DR. GOTTESDIENER: Okay. Thank you very much.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Yes. I had two questions. The first has to do with antiviral resistance. I wonder if either the sponsor or the FDA could tell us about the timing of onset of virological breakthrough. Was it early? Was it late? And what was the clinical significance? Were there any ALT flares associated with this? And how was it managed? What was the algorithm for managing patients who had virological breakthrough?

My second question is actually to Dr. Florian. In the bridging analysis that you

performed to look at late responders, based on your analysis, you presented two treatment paradigms, one to treat with a lead-in phase followed by 44 weeks of triple therapy or to use a lead-in phase followed by 36 weeks and then 12 weeks of consolidation with peg plus ribavirin.

The latter part, I'm being a somewhat vociferous bearing.

Was there any difference in SVR rates in that analysis? That would help me at least in addressing the question the FDA would like us to.

DR. HARRINGTON: I'll first answer the question about resistance. I can't comment on the ALT flares. Maybe Drs. Mishra or Singer could comment on that.

But in terms of virologic breakthrough, most of the breakthrough -- about two-thirds of the breakthrough that occurred in the treatment-naive trial occurred between weeks 12 and 28. There were some breakthroughs a little bit earlier on, but it's sort of varied. There wasn't a clear cut point of one breakthrough absolutely had to occur,

but it appears that most of it was right in the middle of the treatment regimen.

DR. SINGER: And maybe the sponsor can address the second part of that question as far as what happened clinically in patients that had breakthrough.

DR. ALBRECHT: We did not see any ALT flares when the patient broke through. And the trial monitored the patients closely, so we stopped therapy immediately if there was a breakthrough. And I would remind you that a breakthrough was defined as a patient becoming HCV RNA undetectable and then coming back up to 1,000 international units.

We also looked at incomplete virologic response, which I think you're referring to as breakthrough, where they came down significantly and then rebounded back up. And we didn't see any ALT flares in either of those situations.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: I want to get back to the

question of differences or potential differences in the black cohort.

There was a lot that was in the briefing materials that I think set us up to be very concerned about that, and I was initially reassured when I saw the sponsor's data on fibrosis and then to hear your response. But when I look at the slides, there are so few patients and there are virtually no black patients, only five who are METAVIR score F4.

So I'm just wondering what your level of confidence is in attributing the difference in the black patients in the two treatment arms to differences in fibrosis and if there's anything in the literature that might help us to either support that hypothesis or be concerned about that hypothesis.

DR. SINGER: Certainly, we know from many studies with standard of care, peg/ribavirin, that black patients do not respond as well as far as SVR to standard of care. Of course, these differences we were pointing out were not statistically

significant. And when we first looked at them, we noticed that there was a numerical difference, and it raised a little bit of a flag, and we realize that we're talking about subsets of subsets, very small numbers of patients.

So I think in the end, we can't really say what is the optimal duration for those subsets of patients.

Does that answer your question?

DR. ROLAND: I guess it doesn't directly answer the question about how confident you feel in your hypothesis that the potential difference -- I mean, the study is not powered to look at a difference between the two treatment arms, and that's, obviously, the fundamental challenge that we have in trying to decide what is the appropriate duration of therapy for anyone.

But the specific question about given the incredibly small numbers, how confident you are that you can explain the difference in blacks based on fibrosis, because that would make it easier for us, right? Then we just have to look at fibrosis,

we don't have to look at black race.

DR. SINGER: Right. See, we can only be as confident as the numbers we have. They're not large. Perhaps more significant is looking at early responders versus late responders or the treatment week for response as predictive.

DR. MURRAY: And I guess I want to get away from our confidence in this data, because this is really the questions that we're asking you. So it was the sponsor's argument that the cirrhosis makes up the difference between the blacks triple in the RGT arm 2 and 3. We think it's interesting. We note that there are small numbers. But at the end of the day, you have to decide, I guess, risk-benefit for giving more boceprevir for all black patients for a little bit higher SVR versus the toxicity or if you feel comfortable allowing some sort of RGT recommendation for black patients if you can tease out perhaps the groups, the subgroups, that's the poorest responders.

So it goes back to my opening remarks. It's all kind of a risk-benefit based on a lot of

uncertainty in the data, and that's why we're asking you the hard questions. We're trying to present all arguments but don't necessarily look for our confidence in it at this point, because we want the committee's true opinion on these matters.

DR. CARGILL: Thank you. And our last question, if you can be succinct, Dr. Giordano.

DR. GIORDANO: For the FDA. Your analysis excluded 14 patients, and I'd just like clarification. Were those 14 people excluded -- I think you said there was unconfirmed virologic suppression. Was that because it was never repeated or because it was repeated and found to be, in fact, in error or detectable?

DR. MISHRA: Dr. Wen Zeng from our statistics group can answer that question.

DR. ZENG: Wen Zeng, staff reviewer. The 14 subjects have arisen from the week 8 to week 24 or in each, the worst value is inactive, undetectable.

But I think that during the trial, they assigned to the longer duration of treatment. So we think it's early responder -- when we do a

comparison, for the early comparison, we include this subject (indiscernible). That's the reason.

Is that clear?

DR. GIORDANO: I'm sorry. I did not understand your answer.

DR. ZENG: Okay. The question is that these 14 subjects, from the treatment week 8 to week 24, every visit window, they have the viral load undetectable, is not undetectable. So it should be early responder. But during the trial, assigned to longer duration treatment. They should be assigned to the short duration of treatment. It's not just the one-sample or two-sample repeated measures, just different windows.

DR. GIORDANO: So the company can clarify, but my understanding is the 14 patients, at the time they were assigned a longer duration, they were thought to have at least one positive value between week 8 and 24. But on re-testing of the samples, I guess it was determined that they were probably really undetectable if you re-tested the samples, and so might have considered that they

were false positive.

Now, whether to include or exclude those 14 is a judgment call, it is our judgment that they probably should be excluded.

DR. GOTTESDIENER: Correct. And that is correct. In fact, these 14 patients were negative at treatment week 8 and were negative at treatment week 24. The protocol said that if they were positive anytime between treatment week 8 and treatment week 24, they should be assigned to the late responder category.

So, of course, we assigned them per protocol and we did an analysis as they were assigned. But the FDA has pointed out that, in fact, one could look at the same data, as was mentioned by Dr. Murray. It's a judgment call.

In the post-hoc analysis the FDA did, they said you could assign them to early response because they were negative at treatment week 8 and treatment week 24, and they were re-tested -- they're a single value that was above the limit of detection -- was rested and was negative

on subsequent measures. They could just as reasonably have been assigned to the early response category, and so the FDA took them out.

That is the place where we differ, at the per protocol analysis 72 versus 75. The FDA analysis, also a reasonable analysis, is 66 versus 75, and that raises the question of how to treat the treatment-naive late responders.

But we do agree with the FDA, as they showed on slide 52, that if you actually look at the late – sorry -- if you look at the late responders in the treatment failure patients, there they seem to be about the same between the 32 and the 44 weeks of boceprevir. And so the company feels that 32 weeks would be more than sufficient for the late responder treatment-naive patients.

DR. CARGILL: All right. Thank you.

We'll now break for lunch. I can see people shifting in their chairs, so I assume your stomachs have been talking to you during the last part of this meeting. We won't ask you to repeat verbatim what we've said.

We will reconvene in this room again in one hour from now, which is at 1:00 p.m. Please take any personal belongings you want with you at this time, as the ballroom will be secured by FDA staff during the lunch break.

Panel members, please remember that there should be no discussion of the meeting during the lunch amongst yourselves or with any member of the audience.

Thank you, and we'll see you back at 1:00.

(Whereupon, at 12:06 p.m., a lunch recess was taken.)

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

(1:01 p.m.)

Open Public Hearing

DR. CARGILL: Good afternoon.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement,

to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair, and thank you for your cooperation.

Our first speaker will be Martha Saly, Director, National Virus Hepatitis Roundtable.

MS. SALY: So my name is Martha Saly and I'm the Director of the National Viral Hepatitis

Roundtable, and we are a coalition of more than 175 public/private organizations. And some of those are patient groups, medical associations, government agencies, and pharmaceutical companies.

So I do want to mention that Merck is an associate member of NVHR and has provided funding to NVHR at various times in the past and present. They have not paid for my travel here today, though.

We are dedicated to reducing the infection, morbidity and mortality from viral hepatitis in the United States. So although NVHR has really been eagerly awaiting the approval of a new class of hepatitis C drugs, I'm really here today to speak personally as a former hepatitis C patient and as an advocate for people who have not been as fortunate as I.

It strikes me a little bit funny to be able to say I was treated for hepatitis C in the last century. But when I think about what a long road it's been for many of my aging baby-boomer friends who are still suffering from hepatitis C, it seems

totally appropriate to say it this way.

I was diagnosed in late 1998. At that time, there was much anticipation of pegylated interferon, but my doctors decided I could not wait for that. So I embarked on the 48-week journey of three times weekly shots. I was really happy to see that Dr. Poordad is here today because he was my first physician.

I was told that I had about a 30 percent chance of a sustained response, and the word "cure" wasn't even being used at that time. But I decided to chance it. Had I not, I have no doubt that I'd be dead or on a transplant list today.

As I said, I was fortunate. Some would say more than fortunate. Against the odds, I was cured. I'm here today because I believe that something quite historic is really happening here today in this room, and I really want to be a part of it.

For more than 10 years, I've dedicated my personal and professional life to addressing this epidemic. In this role, I've spoken with too many

patients to count who are ill, unable to access the care they need, or who were failed by earlier treatments and who are waiting for something that will give them better odds.

Some just want to tell me their story or tell me how my story inspired them to be able to take the next step. I tell these patients that treatment is not easy and that it has to be a personal choice but one that might save their lives.

It is for these patients that this day is of paramount importance, because for the first time, I can actually tell them although treatment may still be extremely challenging, hope for a cure should outweigh their fear that treatment will fail them.

Yes, I believe that approval of these drugs will be the biggest thing that's happened in the years I've been doing this work and certainly what many patients have been anxiously awaiting. However, I'm still concerned that treatment will continue to be a difficult and challenging goal.

I'm hopeful that a shortened course of

treatment for many patients will equate with a greater ability to tolerate the drugs and manage the side effects, but I fear that the issue of compliance with strict medication regimens might affect treatment outcomes and treatment success. And these drugs will help few if awareness of the hepatitis C epidemic is not increased. And if awareness does not go hand-in-hand with improved screening and affordable access to care for the people who need it, it won't do us much good.

I do have every hope that Merck and Vertex tomorrow --

[Microphone times out.]

DR. CARGILL: Thank you. Yes. We are going to adhere strictly to time because we still have quite a bit of work yet to do. Thank you very much.

Tracy Swan, Treatment Action Group.

MS. SWAN: I'm going to skip the introduction for time, but I do want to say I'm speaking on behalf of Treatment Action Group, a nonprofit think tank where I work. I do not have

any financial relationships with the sponsor or their competitors nor has anyone supported my travel other than my employer.

So I just want to very quickly, obviously, talk about some key issues that are involved with the development program for this drug and frame them in the context of my pleasure at being here for such an exciting and historic occasion.

So as we know, hepatitis C is curable, and we've already heard quite a bit about the benefits of a cure. We've also heard about the grim scenario that patients in the United States face who don't have adequate treatment options.

So if you look at this list, last week there were more than 16,000 people waiting for a liver transplant. And the Phase 3 program for this drug was started in June three years ago, but there have been no early access trials in any extremely ill populations.

I have no doubt that doctors will use these drugs for people without the information that would really support a more well informed treatment

program, and I want to use this as an opportunity to please ask sponsors to consider early access trials for their late stage drugs.

I'd also like to highlight the low enrollment of populations among whom hepatitis C is highly prevalent and also among whom need better treatment, beginning with African-Americans, Latinos and Latinas, treatment-naive, people with cirrhosis, null responders. We don't know if people on methadone or buprenorphine were included in these trials, and we have very little information about the numbers of elderly people who are participants in these studies.

Particularly upsetting for me is a lack of interaction data. There are some high stakes here. There's data in efavirenz and tenofovir, two antiretroviral agents, but the stakes are pretty high. If there as an uncharacterized drug-drug interaction, people could have HIV and/or hepatitis C treatment failure. And co-infected patients have faster progression to cirrhosis and liver failure and really need better treatment, and

they've been waiting a long time.

Methadone. People are at risk for a relapse to active drug use if they're under-medicated or experiencing withdrawal and hepatitis C treatment failure. Transplant recipients risk graft rejection if they are uncharacterized drug-drug interactions with immunosuppressants, as well as antidepressants, the risk for suicide. We know the neuropsychiatric side effect profile of interferon.

I'm surprised that the drug has gone this far without that information, and I hope that in the future this doesn't happen. I also want to make a plea for simplicity. It's very confusing, this data. The trial design is confusing. Interpreting it is confusing.

How on earth is this going to get incorporated into clinical practice, especially for non-specialist providers? We don't even have a treatment guidelines panel to really take this in hand and make it easy for people to optimize treatment.

I am glad that the sponsors and the agency

has thought about the week 24 stopping rule and have thought about ways to modify it. And I'm also glad to see the percentage of people who had an SVR and used EPO, not just the people in the trials who used EPO.

I'd like to close with my list of post-approval trials, which is up there. Thank you.

DR. CARGILL: Thank you.

Lorren Sandt.

MS. SANDT: Good afternoon. My name is Lorren Sandt. I'm the Executive Director of the Caring Ambassadors program in Oregon City, Oregon. I'm also the chair of the National Viral Hepatitis Roundtable that Martha talked to you about earlier. We're a nonprofit patient advocacy group. My company -- my organization does take money from Merck and Vertex. However, they did not pay for my trip to be here today.

I'm here on behalf of my three family members who have hepatitis C, and I'm also here on behalf of the hundreds of thousands of people who are treatment-experienced who are looking forward

to new treatments, and also the millions that are undiagnosed and aren't even aware that we're here today and what we're doing on their behalf, all of us working so hard to make sure they have care when they are diagnosed.

But I do have some concerns. As an advocate, I have spoken with hundreds of patients, and I really have grave concerns about the difficulty of this regimen and the complications within it. I heard this morning the questions that were being asked, and all I kept thinking was, "Boy, if we can't figure it out in this room, how is a doctor in rural Oregon going to figure that out?"

I'm really worried about patients. Boceprevir is not a simple protocol. We know adherence has an impact on treatment outcomes. We heard today we don't know whether it matters whether you take it at seven or nine hours. Patients need to know. So when the FDA comes up with their label, we would really appreciate some really strong guidance on that. There's a lot of

studies out there that show medication adherence is very low just in general. It's at about 50 percent. And if you add depression or if you add any other co-morbidities, like diabetes or HIV, which many hepatitis patients have, the regimen is going to be increasingly difficult. And whenever you have a long, complex regimen, it really changes the adherence picture. So I'd like to see for the patients not to get resistance and to be best managed, to really have some strong guidance on adherence.

Clinicians must incorporate supportive services and they need to learn what those supportive services are. We need some guidance on that. In HIV and TB, we have directly observed therapy. That does not exist. There's no one who's going to go home with a hepatitis patient and make sure that they took their drugs. Those case managers don't exist in hepatitis.

Alternative therapies. One of the most widely used alternative therapies in this country is milk thistle, and it's certainly used within

hepatitis C patients. And I'm really concerned about the lack of data since milk thistle and some protease inhibitors share the same metabolic pathways. Patients and providers need this information, so I'd really like to see that study done.

As has been mentioned previously, special populations are really a concern for all of us. The FDA recently came out with their strategic guidelines and said that addressing unmet public health needs of special populations is a priority. And what I saw here today, we need to do a lot more work on those special populations.

One that was not talked about today that I'd like to bring your attention to is the co-infection with hepatitis B. It's estimated that up to 30 percent of people with chronic hepatitis B have hepatitis C, and 8 percent of the chronic hepatitis C patients in the VA have hepatitis B. What is going to happen when we give them a protease inhibitor? What's going to happen to their viral titer.

EPO. How are cash poor Medicaid states going to pay for EPO on top of the cost of all of these other drugs? It's not going to be an option for many people who are on not first tier insurance programs? So I want to make sure that those people have the best chance of getting cured, as well.

So I thank you for your time. Really looking forward to all of these --

[Microphone times out.]

DR. CARGILL: Thank you for sharing your remarks.

Michael Ninburg?

MR. NINBURG: Good afternoon. My name is Michael Ninburg. I am the Executive Director of the Hepatitis Education Project, a nonprofit organization based in Seattle, Washington. Our organization has received funding support from both Merck and Vertex.

I was a hepatitis patient myself for many years until May of last year when I learned that I was cured after a course of 48 weeks of treatment. I had been diagnosed about 20 years ago and

initially sought treatment about 10 years ago and was given the prognosis of about a 50 percent likelihood of cure. I was also told that newer, better drugs would likely be available within five years.

Well, as we know, that timeline proved to be optimistic. In the meantime, my liver disease did progress. I eventually did progress to borderline cirrhosis and was told that it would be a good idea to enter treatment. I was fortunate enough to get into a clinical trial about two years ago, and, as I mentioned, I am now cured.

I'm here today to advocate on behalf of approval for boceprevir. That said, I do have some concerns, all of which have been addressed here today, but I will point out a few. Among them, further study is certainly warranted among drug-drug interactions.

The effect of boceprevir on methadone and buprenorphine, in particular, is one of the more important areas for study, especially given that most new hepatitis C infections in the U.S. are

related to injection drug use and many of those persons who are newly infected will eventually go on to opiate substitution therapy.

Similarly, as has been pointed out already, drug-drug interaction studies are very important for antidepressants. This is crucial because we know that other protease inhibitors do reduce exposure to some SSRIs. And because depression is such a common side effect for treatment, more and more patients are being given antidepressants prophylactically before initiating treatment.

Proper management of side effects will also be crucial to ensure that patients have the best chance of being cured, and I do look forward to seeing the results of the studies underway looking at the EPO versus dose reduction to address anemia.

I would finally like to reiterate that adding boceprevir to peg/riba with a lead-in and response-guided therapy is going to make a complex treatment regimen even more complex. This will be equally true for patient and provider. Adding to the complexity is a fact that providers who treat

hepatitis C are generally inexperienced with drugs that can cause viral resistance, and this has been pointed out, as well, today.

Adherence will be crucial to successful treatment, as will effective mitigation of side effects. For these reasons, labeling recommendations should be as specific as possible.

This is truly a watershed moment in the treatment of hepatitis C. The drugs you are reviewing today and tomorrow will increase the cure rate for patients and, equally importantly, reduce the length of treatment for many patients. This is the first real breakthrough in treatment in the past 10 years and is the next step toward a universally effective cure for hepatitis C.

Thank you.

DR. CARGILL: Thank you.

Jules Levin?

MR. LEVIN: I believe most of you know just who I am, and I have a few comments. The first thing I want to say is I read all the briefing documents and listened to the FDA presentation, as

well as the Merck presentation, so I think I'm fairly familiar with the data.

I want to say that I do support, for a change, the FDA position on the 32 weeks. I think that we need longer therapy for certain patient populations, the harder to respond patients. So I'm in full agreement on their analysis on that. And I want the committee to know that I support that, and I think it's a good thing for patients. A little extra therapy is better than too little therapy for patients who are hard to treat.

I want to talk about the null responder situation a little bit, and what I'd like to say is I think that it's a fluid situation, it's a difficult situation. And I think that what might be helpful here is perhaps for the FDA to put some language in the label about null responders, maybe without taking the position that supporting treatment or not supporting treatment for null responders. But maybe some language about what we know, what we don't know, the strength of the data, the weakness of the data, because what does concern

me is some patients who are null responders who maybe can't wait too long for new drugs to come along.

So I don't want to deny them the opportunity. At the same time, I don't want to treat somebody unnecessarily that could wait. So maybe some language would help, if you could do that. Maybe you could comment on whether you can just put some language in there that would help people interpret things.

I want to talk about co-infection and DDIs, drug interaction studies. I'm a little disappointed perhaps. Maybe Merck and the FDA could fill us in a little bit about what has been done in co-infection, what has -- maybe Merck could explain a little more about what they've been doing in co-infection and what their plans are or what they have done in drug interaction data, because we're going to hear Vertex's data tomorrow; we know what that is in drug interactions and co-infection studies.

What does concern me is that there are

patients with co-infection that really can't wait too long for new drugs to come along, and if they're not on Reyataz or telaprevir, what are they to do? So I'm concerned about that.

Then lastly, the last point I want to make, I would love to hear some discussion from Merck and the FDA and Vertex tomorrow. We know how complicated this is becoming now in terms of therapy and how difficult this is going to be for patients and clinicians to understand how to do it and what to do.

I really would love to see better education programs from the companies and the FDA to help us on this for clinicians and patients about understanding resistance. I really don't want to hear companies saying, "We won't have resistance. It's going to disappear, and you can re-treat," because we really don't have an answer to that question. That could happen but we don't know.

So what I'd like to hear is some real education for clinicians and patients not just about resistance but about adherence, about all the

stuff that we need to know about coming in at week 4 or week 8 to do your viral load testing and why that's important. There are many, many issues that I could list here, but what we need is better education programs from the companies and the FDA to support this and encourage this and perhaps to demand it from all the companies as we move forward here.

Lastly, I just want to comment on early access.

[Microphone times out.]

DR. CARGILL: I'm sorry. We have to keep moving forward. Thank you.

Murray Penner?

MR. PENNER: Good afternoon. My name is Murray Penner, and I'm the executive director at the National Alliance of State and Territorial AIDS Directors, or NASTAD. Neither NASTAD nor me have a financial relationship with Merck. NASTAD does receive money from Vertex, but they did not pay for my travel here.

NASTAD is a nonprofit organization that

represents the nation's chief state health agency staff who have programmatic responsibility for administering HIV and viral hepatitis education, prevention, care, supportive service programs funded by state and federal governments.

I'm pleased to have the opportunity to speak briefly about your consideration of this new drug application for boceprevir. While not necessarily in the purview of the Antiviral Drugs Advisory Committee, I must point out some very important considerations regarding this new treatment and the public health infrastructure that will impact access and uptake of this drug.

Given the lack of public health infrastructure for viral hepatitis and the many barriers to care for persons living with chronic hepatitis C, the cost of this new treatment will significantly impact affordability and comprehensive coverage of patients.

NASTAD encourages Merck and the FDA, as well as other government agencies, to work together to ensure that uninsured and underinsured patients who

need treatment are able to afford the drug, as well as the entire standard of care, given that this new treatment will be added to and not replace the current hepatitis C standard of care. Further, coverage must include ancillary medical costs, such as liver and viral tests, liver biopsies, and management of treatment side effects.

As you know, this treatment will not eradicate hepatitis C. A cure must rely on infrastructures, such as funding for screening and testing, staff capacity in medical settings, and educated health providers in order to identify those who need treatment in the first place.

In order for this new treatment to work, new diagnoses are required. Unfortunately, as you know, 75 percent of people living with chronic hepatitis C, or up to three million people, do not know they are living with infection and must be identified.

The IOM recently reported a lack of knowledge and capacity among providers to identify infection and deliver expert care, as well as a

lack of knowledge among the public, most importantly, among populations at high risk of infection. Even with this new treatment, low provider awareness will continue to lead to lower than anticipated utilization of this drug and misdiagnoses.

In addition, there are limited specialists, such as infectious disease doctors, hepatologists, and gastroenterologists available to treat hepatitis C. Further, low public awareness will continue to lead to misinformation and missed opportunities for prevention and care.

Targeted and difficult to reach populations must have access to this new drug, as well as appropriate care. Treatment will need to be given in tandem with other important public health and social services being provided in public health settings.

If we do not capture the 75 percent of persons living unknowingly with chronic hepatitis C, the costs associated with liver cancer caused by chronic hepatitis and the care and

treatment of persons living with chronic hepatitis are very high. In the absence of significant increases in screening and care above current medical management, an actuarial study from Milliman, Incorporated projects medical costs for patients with chronic hepatitis C will go from 30 billion to over 85 billion over the next 15 years.

Finally, further post-marketing studies of this drug must be conducted in order to further define potential risks, other drug interactions, and impact on certain populations, including blacks, where there is evidence of lower sustained virologic response.

Thank you for the opportunity to provide comments this afternoon.

DR. CARGILL: Thank you.

Paul Brayshaw?

MR. BRAYSHAW: Hi. My name is Paul Brayshaw. I'm here on behalf of people with bleeding disorders, and I have no conflicts to report.

We're a group of people who are made up of patients and supporters who were affected by the hepatitis C crisis. We organize and advocate for urgent development and access to new, far better HCV therapies. As stakeholders, we salute the efforts of the FDA for their early approval of telaprevir and boceprevir, and we appreciate the proposed guidance regarding the testing of the direct acting agents, and, more positively, guidance regarding drug combination testing.

Our campaign has been recognized and is supported, in part, by the Hemophilia Federation of America, the National Hemophilia Foundation, and the Committee of 10,000. Among people with factor-dependent bleeding disorders over the age of 30, nearly the entire cohort was exposed to hepatitis C via contaminated factor. As a result, most of us now have long-term disease associated with these products and therapies which were used for the treatment of bleeding disorders.

We support the earliest possible approval of the drugs, telaprevir and boceprevir. However,

people with bleeding disorders have specific problems with hemostasis or the ability of the body to stop bleeding, which may be further exacerbated by hepatitis C and HIV disease, as well as HIV therapy. Standard of care therapy for hep C also depresses hemostasis, and while the next generation of hepatitis C therapy is becoming available, those could potentially have other complications, as well.

People with bleeding disorders and hep C also have high levels of HIV co-infection which is associated with faster hep C progression and a decreased likelihood for hep C drug therapy success. The FDA should require advertising and/or educational materials on these drugs, as well as define difficult to treat populations and point out that treatment success rates for these groups may be substantially lower than those pertaining to the population as a whole.

We also request the FDA require guidance and warn about treatment failures with the next generation of drugs, as well as the leading into

resistance among the most endangered and difficult to treat populations.

The medications for the treatment of bleeding disorders are extremely expensive. On average, they cost approximately 100 to $150,000 a year for insurance companies, and that has an impact on patients, as well. Employer-based health insurance or some other form of health insurance is critical to ensure access to these life-saving therapies, and we encourage the FDA, the pharmaceutical companies, as well as insurers to recognize this burden in the context of additional chronic illnesses. We are concerned that this affordability issue may affect access to therapy, as well as adherence.

Our efforts have been collaborative, transparent, and with dedication, because our lives depend on the development and access to more efficacious therapy. And so we call on the FDA to protect us from advertising or educational materials with the promise of a high cure rate, as well as treatment success as treatment becomes

available.

Thank you.

DR. CARGILL: Thank you.

Dr. Belperio?

DR. BELPERIO: Hi. I'm Pam Belperio. I'm the national public health clinical pharmacist for the Department of Veterans' Affairs' Office of Public Health, and I'm here to talk to you today about the VA experience with hepatitis C.

This presentation will summarize the VA's experience with real world diagnosis and treatment of chronic hepatitis C over the last decade. We hope that this data will be useful to the committee in discussions about these promising new therapies, particularly with regard to populations for which more data may be helpful in assessing safety and efficacy.

As seen in the chart on the left-hand side, chronic hep C has been a major clinical and public health issue in the VA over the last 20 years. Veterans have a hep C prevalence rate over three times that of the general U.S. population and even

higher prevalence in certain high risk populations, such as homeless.

In 2009, the VA had roughly over 210,000 veterans in care seropositive for hepatitis C and approximately 157,000 with chronic hep C, representing 5 percent of all individuals in the United States with chronic hep C. The VA has a sophisticated infrastructure for hep C policy, programs and products to achieve the highest possible outcomes. As a result, over 80 percent of veterans with chronic hep C have been linked to care.

Despite this infrastructure, the reality is that most patients with hep C do not receive treatment. Whether the setting is in the VA, community practice or academic medical centers, the most common reasons for exclusion are psychiatric disorders and alcohol and substance abuse disorders.

The reality is that many patients have significant co-morbidities that wouldn't qualify for clinical trials based on exclusions, and I'd

like to focus on this for just a moment because these patients represent the majority of hep C patients in both the VA and non-VA settings and, in many ways, are those patients who can benefit most from these new therapies.

Understandably, registrational trials have excluded these patients, and while it's appropriate, it's important to keep in mind that we do not have safety and efficacy data on hep C protease inhibitors for significant populations of hep C patients in need of treatment and that the benefit-risk profile may differ in these individuals from those enrolled in clinical trials.

Yet, we often treat these patients regardless with little knowledge about what we can or should expect in terms of efficacy, safety and tolerability, as you can see here. As a result, we often see more adverse effects, higher discontinuation rates, and more dose modifications.

As a consequence, we have observed SVR rates that are, as one would expect, lower than seen in registrational trials. And this should not be

surprising to anybody in the audience, as real world populations outside of those studied in registrational trials show different levels of benefit. But we clinicians in the field and patients need guidance on what to expect in terms of efficacy and safety in these not so ideal, yet all too realistic populations so that reasonable, evidence-based discussions can take place between providers and patients with a practical understanding or at least some insight into the risks and benefits of treatment.

I want to thank our colleagues at Merck, Vertex, and the FDA for the hard work in getting us to this point. These new therapies promise a paradigm shift. Yet, at the same time, it's important to recognize that efficacy in a clinical trial is not the same as real world effectiveness and that we're treating patients, not just a virus.

We look forward to the discussion about what the next steps should be in studying populations who have yet to be enrolled in clinical trials.

Thank you.

Questions from Committee to Sponsor and FDA

DR. CARGILL: Thank you. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the committee, as well as the public comments.

We're going to return, because we had to cut our questions short in both parts of our discussion, so we're going to return to questions, which will be for either the sponsor or the FDA or both.

Dr. McGovern?

DR. MCGOVERN: Thank you. I'd ask the sponsor to give us some slides about whether four-week responses to interferon predict 12-week responses. And this was supplied with the documents. So if we could have that slide, I'd just like to look at that data again to refresh my memory.

DR. GOTTESDIENER: Yes. If we could see

slide 550, please. Thank you. If you can show this slide.

So this is a slide, and we have one subsequent slide to do the analysis that was requested earlier in the day to look at this same kind of concordance data at the 0.5 level at treatment week 4, which we would like to share with the committee, as well, since it was requested.

What this slide attempts to do is to help people to understand how comparable are and how much overlap there is between the two populations, the two definitions for null responders, treatment week 12 and the treatment week 4; treatment week 12 less than 2 log and the treatment week 4 less than 1 log.

What you can see is in the center is a 2by2 table, and this data is from the IDEAL trial, which had 3,000 patients. And we took this data, though similar data is available for both SPRINT-2 and RESPOND-2 for smaller numbers of patients, because this has a much larger cohort of patients who receive standard of care. So we could really see

how these two definitions line up.

In the top left, you see 533 patients who met both definitions, both the less than 2 log at treatment week 12 and the less than 1 log at treatment week 4. And remember, because this is PR, because this s standard of care, every patient could be fully defined as to being one or the other of those definitions, something that isn't always possible in the boceprevir-treated patients.

If you look at the bottom right for the diagonal, you see the number 1926, which are patients who were greater than 2 logs in terms of treatment week 12, who are not null responders, and who also did not meet the treatment week 4 definition overall. And on the diagonals, you can see 172 patients and 146 patients who either met one of the definitions or met the other of the definitions.

In practice, with this particular population, depending on which study you look at, somewhere between 65 and 85 percent of the patients are exactly the same patients. So in other words,

whether you define them by a treatment week 4 definition or whether you define them by a treatment week 12 definition, they're exactly the same patients.

If you could put up the slide that's done the analysis at treatment week 4, slide A1, please.

This is the same study analyzed by the treatment week 4 definition of 0.5. Remember, the FDA proposed that definition to come up with a definition that was more stringent, that really used a treatment week 4 definition that totally identified null responders. And you can see, from the IDEAL trial, they've actually succeeded.

If one looks across the row that says "less than 0.5 log," one can see that out of 253 patients who meet that definition, 234 of them, 90 percent, actually are the same patients who would have met the same definition for a treatment week 12 responder, a null responder. And there are only 19 patients, if one looks to the right, who really are discordant in terms of the treatment week 12 and the treatment week 4 definition.

Before we go any farther, I want to remind everybody that the FDA has analyzed that particular definition in our trials -- they showed that in the slides -- and those patients had 28 to 30 percent response rates with boceprevir as opposed to zero in the control arms overall. So if one uses that definition, again, it's an alternate definition of poorly interferon responsive patients, one can see, in fact, they do identify exactly the same patients, at least 90 percent or so, and there's still 28 to 30 percent, increased percentage, with boceprevir.

As the FDA did point out, it is a more stringent definition in the other way. If one looks down the column of less than 2 log, it only identifies about 30 percent of the true null responders. So this definition is a very stringent definition of null responder, the most poorly interferon responsive patients. And even so, it's still a very useful definition to help to understand that there's great concordance between the two definitions. And therefore, this data

supports the 30 percentage points increase in the null responders.

Thank you.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I was just looking at those slides, so it brings up a similar question. I wanted to make a point initially that we've changed the definitions on a lot of things. So we're calling a null responder something different. You approach that in your slides there.

These patients and the patients in your PROVIDE study are naive patients, correct?

DR. GOTTESDIENER: The patients in PROVIDE are all patients who failed in the -- PROVIDE included many patients, but the ones we provided in the analysis are all patients from either study who failed on the control arm, met the definition of null responder, and then proceeded through 44 weeks of therapy.

DR. STRADER: Okay. And there were 38 of those, but you say failed on either.

DR. GOTTESDIENER: Could have failed in either from RESPOND-2 or from SPRINT-2 control arms.

DR. STRADER: So RESPOND-2 was non-responders.

DR. GOTTESDIENER: Correct.

DR. STRADER: Right. So those would be partial responders and relapsers in that group that would have been in the control group that you would have put in your PROVIDE study.

So do we know how many of those 38 patients you had came from the RESPOND control group as opposed to the SPRINT control group?

DR. GOTTESDIENER: Yes. I'll have the slide up in a minute. But I do want to clarify one thing that actually is incorrect about what you said.

While, by historical definitions, we only brought in partial responders and relapsers, we know from looking at the control group in RESPOND-2 that we didn't succeed in that particular goal. So in RESPOND-2, as we showed in the briefing booklet, 20 percent of the patients, despite that

exclusion, demonstrated themselves as being null responders by hitting less than 2 logs at treatment week 12.

So I want to be very careful. The historical definitions are useful tools, but in practice, despite all the efforts we made to keep patients out of that particular trial who were null responders, 20 percent of them came into the control group and demonstrated in the course of their control therapy.

Now, if you actually want to look at the data you asked for -- show slide 566 please. This actually breaks the data down by the 38 patients by which study they came from. And what you can see if you look down the left-hand column is the 29 patients who came out of the SPRINT study and the nine patients who came out of the RESPOND-2 study, all of whom who met the definition of null responders in the control arm. And you can see the SVR rates are 34 percent and 56 percent.

I would caution these are very small numbers. That's why we took the two groups

together and we compiled it as 15 of 38, the last column, which really is the pooled data.

I hope that helps to clarify a little bit.

DR. CARGILL: Thank you.

May I just caution the committee, because we have a number of people with questions, if your questions can be targeted, as well as the answers succinct, it would be helpful.

Dr. Korman?

DR. KORMAN: My question relates to the other side of the equation, not the benefit, the sustained virologic response, but the risk.

Do we have any idea from the FDA or the sponsor as to the distribution of risk, side effect profile based on age, gender, fibrosis score, co-morbidity or race so that we try to get some sense of the risk stratification that a clinician might have to do in terms of interpreting which patients they're going to try to treat and which they may decide to delay?

DR. MISHRA: The sponsor has presented some data, and we have also looked in the analysis,

response-guided therapy versus long duration boceprevir, and we have seen that there is some difference, there is some benefit of having a shorter course of boceprevir in terms of anemia, in terms of serious adverse events and discontinuations.

So we do feel that a shorter course of boceprevir therapy may provide a favorable benefit-risk assessment.

DR. KORMAN: Within the groups where we've had these profound effects, the very unique events, is there any guidance in terms of which population or which subgroup? I understand that shorter is better, but is sicker worse?

DR. SINGER: So if you look at the data comparing the treatment-naive and treatment-experienced populations, there were generally more serious adverse events, severe adverse events in the treatment-experienced population. It probably goes along with their stage of illness; although if you look at subgroups, there did not appear to be any difference in safety profile, for example, by

age, by gender, by race.

DR. CARGILL: Dr. Ghany?

DR. GHANY: I guess this was just to try to address a question that I had that wasn't answered in the earlier session. It was to Dr. Florian.

The question pertains to the bridging analysis that was performed and based on that analysis, the FDA proposed two treatment regimens for late responders, one using lead-in with 44 weeks of triple therapy versus lead-in with 36 weeks and then 12 weeks of consolidation with peg plus ribavirin.

The specific question was what were the SVR rates for those two different regimens? Thank you.

DR. FLORIAN: To that question, we have the SVR for the 32-week regimen. It comes from the treatment-experienced trial, but this is a group that only had prior relapsers and prior partial responders. So in a treatment-naive setting, it may be a little bit lower than what was seen there. We're not entirely sure what the difference in a treatment-naive late responder setting would be

between the two regimens, but we do know that 32 weeks or extending it to 32 weeks would cover a majority of that numeric difference that was seen from the treatment-naive late responder arm.

DR. GHANY: What were the actual rates?

DR. FLORIAN: Oh, the actual numbers.

DR. GHANY: Yes.

DR. FLORIAN: So from the treatment-experienced arm, the RGT, so the one that looked at 32 weeks, 79 percent. For 44 weeks, it was 73 percent. And then for the treatment-naive late responder arm, where they looked at 44, it was 75 percent.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: I have two quick questions. You used a last observation carried forward method and stated in the background materials that there was a very small number of people who were lost to follow-up after week 12.

Can you address what the numbers were and whether there were any differences across arms in

either of the studies? That's question number one.

Question number two is, do you have a list prepared of the CYP3A4 substrates with narrow therapeutic index that we could take a look at?

DR. ZENG: This is week 12 follow-up carried forward for subjects who missed week 24 follow-up. It's pre-specified in the protocol, and this is a pre-specified analysis.

In terms of number of subjects, I can get a number to you later, but the number is very small, and we did sensitivity analysis, and probably the sponsor can give you the exact number. The numbers are very small. I can dig up for you.

DR. ALBRECHT: Could you bring up slide 291?

This slide gives you a comparison in the SPRINT-2 study of using the last observation carried forward. On the left side is the SVR for follow-up 24 and in the parentheses, missing equals failure when we do all of these studies. And the second row is SVR last observation carried forward.

Arm 1 is the peg/ribavirin control. As you can see, the response rates are almost identical,

37 and 38 percent. You can also see in arm 1 that they're 62 and 63; and, in the third arm, 65 and 66. So there were very, very few patients that were carried forward. There were four in arm 1, four in arm 2, and three in the arm 3 study.

So we had a very good return on our patients coming back for their week 24 follow-up, and there was no difference essentially in the SVR rates.

DR. CARGILL: Thank you.

Dr. Connick?

DR. CONNICK: I have two general questions. The first relates to conception. What were the instructions given to males and females about birth control in the study? How many pregnancies did occur and what were the outcomes?

DR. ALBRECHT: Using the backbone therapy that we used, the peg/ribavirin, ribavirin is a teratogen, and we used the same criteria that is in the label of double-barrier contraception in the study. We required that patients use it prior to the start of the study and during the follow-up period. There were no pregnancies in patients that

were being treated. There were pregnancies in partners, and those are reported in the ribavirin registry. There were no outcomes in partners to suggest that there was any ill effect.

DR. ROLAND: Thanks.

My second question is adherence. You said you did have adherence measures in the study. These are very difficult drugs to take. What was the level of adherence in the two studies?

DR. ALBRECHT: We used an electronic diary to have the patient record their medication. They recorded all three medications and did so on a daily basis. The electronic diaries were taken to the site where they were uploaded, and that's the way we collected the data.

Could I have slide 2632 please? This slide is illustrative of SPRINT-2, and it shows you that the level of adherence that was reported to us was basically very, very good. We found that in looking at SVR, that treatment duration was actually more important than dose. But as you can see on the left side, treatment duration greater

than 80 percent, dose of ribavirin and boceprevir greater than 80 percent, most of our patients are in the more than 80 percent range.

DR. ROLAND: Thanks.

DR. CARGILL: Ms. Young?

MS. YOUNG: I'd like to congratulate the sponsors for coming through with a breakthrough item, but I am concerned with some of the issues raised by the public groups in terms of complications of this regimen and wondering if you could give a little more description of what the response-guided therapy looked like in the trials. And then if the FDA could tell us what they're thinking of in terms of guidance, in terms of protocols for physicians to make sure that once these drugs do get into the system and there's demand for it, that they actually have a positive effect and are used appropriately.

DR. GOTTESDIENER: If I could see the pathology slide, slide 118, please?

This is the kind of slide -- obviously, there needs to be very good educational materials,

as we've heard before and as we all acknowledge. This would be the kind of slide that would be available to practitioners, obviously, in a more patient-friendly or in a practitioner-friendly manner. But it lists all of the different groups and what the durations of therapy would be for treatment-naive and treatment failure, early responder and late responders.

MS. YOUNG: As a follow-up to that, in terms of the use of EPO, is that going to be part of the instructions?

DR. GOTTESDIENER: In our studies, we did give instructions for EPO, and I'm sure we'll have some very interesting discussions with the FDA about what will be included in the label. But we certainly think that that's an important part of the instructions to practitioners.

DR. CARGILL: Thank you.

Dr. Schechter?

DR. SCHECHTER: A question more about the hematologic safety. You showed us a hemoglobin decline and neutrophil decline with timing. The

same decline in terms of timing for the grade 3 and 4, are they similar?

I also wanted to know what the directions you gave -- that is, how often were CPCs counted, that is, tested for? And given the complications that you've seen in terms of the severity of the anemia, whether those will be enhanced; that is, should people be tested more frequently during certain periods of time?

DR. ALBRECHT: The peg/ribavirin label has actually a warning about anemia and the peg/ribavirin label states that at week 2 and week 4, the patient should be tested and more frequently if clinically indicated. This was also the way that we did it in the clinical trials. Now, in the clinical trials, patients were tested at every visit or as clinically indicated. So some patients, if they had steep declines in hemoglobin or neutrophils, were tested more frequently.

With regard to your second question, we do have -- probably the best indication was in the slide that we showed you, 89, with regard to

hemoglobin values during treatment and when we saw the nadirs. As we indicated, those hemoglobins dropped very rapidly in the first four weeks and then we saw the decline after that. So we were catching them as they came in on the various clinical visits. So a physician watching a patient would be calling them back if they were seeing a steep drop in hemoglobin.

DR. SCHECHTER: So you're not thinking that one should treat -- one should be testing weekly in that period of the 8 to 12 or which -- one wonders if one could avoid the grade 4 particularly in the neutrophil and platelet.

DR. ALBRECHT: The directions and the protocols were that if the hemoglobins or the neutrophils continued to drop, that the patient should be called back. So if the hemoglobin was dropping and there was a hemoglobin that was close to 11, one would expect a physician then to call that patient back the next week. And the physicians, at their discretion, could call the patient back as many times as they felt was

appropriate.

So those grade 4s generally -- as you could see, there were not that many grade 4s. Those hemoglobins were caught before they got down to a grade 3 or a grade 4.

DR. SCHECHTER: In the patients who had more anemia, as in the blacks, particularly in the blacks, who often start at a lower hemoglobin level than Caucasians do, the question was did they have more ribavirin reduction and did that possibly account for the lower SVRs?

DR. ALBRECHT: I'll start from the SVR perspective first, and that is, blacks do have lower SVRs with two-drug therapy. And using the base that we're using, the peg/ribavirin backbone, it's not surprising that with boceprevir they have lower SVRs.

We know for some reasons why they have lower SVRs, IL28 being one of them. But if you look at the difference in SVR from the control with boceprevir in the blacks, the delta from the control is almost the same as we see in the non-

blacks. So the SVRs are not so much related probably to their anemia as to other facts that are associated with the black race.

I think Dr. Bacon will comment on the anemia and the way he manages anemia with these drugs.

DR. BACON: Thank you, Jan.

I'm Bruce Bacon. I'm at St. Louis University. That's the people who pay me. I am a consultant for a lot of pharmaceutical companies and my travel expenses were paid today by Merck.

I think that the management of anemia, for anybody that has a little bit of experience with taking care of patients with hepatitis C on interferon and ribavirin will be comfortable handling the anemia, the leukopenia or neutropenia, and thrombocytopenia that we see with these regimens when they add boceprevir. I really don't think it will be that much different for most of us.

It's comforting to know that there's good data that shows that you don't lose the ability to attain a sustained response by dose reduction of

ribavirin, which is -- some people brought up the question about, oh, we're going to have to use all these erythropoietin that's so very expensive. Well, there's data that shows that you can do just as good a job with dose reduction of ribavirin and not lose that effect.

So there's a lot of different strategies and ways in which these complications can be managed. But anybody that's done this for a little bit knows how to do that. I don't think it'll be very difficult.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: Just to follow-up on a theme, my question had to do with the role of IL28B genotype testing, which I realize came out while you were doing your studies. But I wonder to what extent this impacted the differences in racial responses and, also, how you see that ultimately fitting into practice in patients treated with three-drug therapy, further complicating the management for the practitioner.

DR. ALBRECHT: We found the IL28 genotype in the IDEAL study, and the IDEAL study had started before we initiated -- the IL28 was found after we had initiated our trials. So, basically, we had collected pharmacogenomic samples in the two trials, the SPRINT and the RESPOND-2 trial, and there were 60 percent of our patients who had agreed to give pharmacogenomic samples. So we only have a partial set of IL28 data. And in cooperation with Duke, we also looked at the IL28 in these studies.

The distribution that we found in the two studies of CC, CT and TT were very similar to what we saw in the IDEAL study. So the proportion of patients that had these different alleles was quite similar.

With regard to the response with regard to IL28 -- if I could see the slide with -- yes, 642, please. This is the data from SPRINT-2, again, as an illustration of SVR by IL28 genotype. And in the white are the controls, in the yellow, the response-guided therapy, and in the orange the

boceprevir 48 weeks. Now, I will caution you this is a retrospective analysis. It's only part of the data, but it does illustrate what we've seen before.

In the CC allele patients that received peg/ribavirin for 48 weeks, they do very well. And as you can see in the response-guided therapy in the boceprevir 48-week group, when you add boceprevir to the mix, they also do very well with the CT and the TT patients.

I would call to your attention, however, that in the response in the 48-week group, with two-drug therapy, it's a 48-week therapy, and we know that the CC patients that are treated with boceprevir, that 70 to 80 percent of them are in the early responder group.

So if you treat a CC patient with boceprevir, they are very, very likely to be an early responder, get 28 weeks of therapy, and be done with their treatment in 28 weeks as opposed to -- they do also respond well with 48 weeks of peg/ribavirin.

DR. CARGILL: Okay. Thank you.

Ms. Valbh?

MS. VALBH: I have a couple of questions about the anemia.

What percentage of patients were on EPO and GCSF at the same time? And then out of that, what percentage stopped therapy because of compliance?

DR. ALBRECHT: We do not have the data on the combination of EPO and GCSF. But if you remember from the GCSF, there wasn't very much of it used. I think it was 9 percent. So it was relatively low.

I can't comment on the compliance with regard to the use of GCSF and EPO because we didn't collect that.

MS. VALBH: And, in addition, what percentage of patients -- it seems to me, with the anemia -- I'm a little confused on the magnitude of the hemoglobin drop, because if a patient came in with a high hemoglobin and they were at 18 grams per deciliter, for example, and they dropped to 14 grams per deciliter, it's unclear, because it

was at the discretion of the investigator to report that as an adverse event. And if they intervened, then it was reported as an adverse event. So it's not very clear to me exactly how much the hemoglobin was dropping based on the addition of the triple therapy.

Can you comment on that?

DR. ALBRECHT: We looked at -- and I believe the FDA did the same thing. We looked at the hemoglobin in two ways. We looked at the hemoglobin reported as anemia, which was, as you said, the investigators' discretion or responsibility to report that as an adverse event. But we also showed you the data for -- the lab data by hemoglobin grade.

So if you look at the concurrence between the two, they're actually quite close, because investigators that were reporting anemia, basically, less than 10 grams, was matching the laboratory data fairly closely.

DR. CARGILL: Thank you.

Dr. Giordano?

DR. GIORDANO: Two, I think, quick questions. First, could the sponsor please describe the exclusion criteria related to depression or psychiatric illness? And second, on the IL28 question, given this very small number of black participants relative to the overall study populations, were there any analyses done to see if IL28 genotype explains the differential response in the black patients?

DR. ALBRECHT: We'll start with the depression. We have in our protocols exclusions for patients with severe depression or a history of severe depression. So, for example, patients with a history of hospitalization for depression would have been excluded from the trial.

The protocol also had guidelines to reduce the peginterferon if depression became moderate, to stop the interferon if the depression became severe, and there were guidelines around also tracking the patient from the concept of calling them if they have reported depression or having them come in more frequently. And if the patient

had severe depression, all three drugs were stopped.

DR. GIORDANO: How was depression assessed? Was there a quantitative assessment or was it purely subjective?

DR. ALBRECHT: It was the investigator's assessment of the patient or the investigator's assessment of the patient in cooperation with a health care professional if he sent them to another physician to be evaluated.

We don't have the analysis of IL28 in the black patients.

DR. CARGILL: Thank you.

If you could just state your name into the record, please.

DR. PACANOWSKI: Mike Pacanowski, genomics group. Essentially, there were a very few number of black subjects in the treatment-naive trial that had IL28B genotype data available. So the total numbers of black subjects who were CC was 16, CT was 40, and 38, which is the low responder genotype, TT; there were 38 subjects.

The response rates, even despite the low number of subjects, did track in the expected direction, being incrementally lower in subjects who had one or more copies of the T.

DR. GIORDANO: Were they still lower than the non-black population, or when you adjusted for that, did it even out?

DR. PACANOWSKI: It's very difficult to tell just given the very small sample sizes. So you're dealing with 5 to 10 subjects in each of the treatment arms. So it's very difficult to rely on the percentages and estimates from that.

DR. CARGILL: Thank you. That's helpful.

Dr. Knodell?

DR. KNODELL: I have two questions for the sponsor. Slide 107 says that the sub-analysis shows that the safety profile with CYP3A4 substrates or inhibitors was similar when administered with boceprevir.

Now, I do a lot of endoscopy. We use a lot of midazolam. A fivefold increase in AUC, it seems to me, would probably keep somebody on boceprevir

asleep for a couple hours after an EGD.

The second question is, you talked about futility, and all through the previous discussions and your data, futility was positivity at 24 weeks. And then somewhere during the presentation, the question of calling futility a 12-week 100 international unit level of RNA was raised. And I wondered if there was some support for that or why that was inserted.

DR. ALBRECHT: I'll let Dr. Kasserra answer your first question, and then we'll go to the futility rule question.

DR. KASSERRA: We did do sub-analyses within the Phase 3 of the CYP3A substrates that were administered with boceprevir. They did, in fact, include midazolam. What we did not collect was the dose that was taken or the timing of the dose as compared with the doses of boceprevir.

We did not see any unusual or remarkable safety profile with any of the CYP substrates that were co-administered with boceprevir. With midazolam specifically, generally, patients did

take, for example, one dose, and it was impossible to tell from the data we collected whether, for example, they slept two hours longer.

DR. ALBRECHT: We'll turn now to the futility rule. As Dr. Gottesdiener mentioned, in cooperation with the FDA and the scientific consultants that we engage, we have been looking for an earlier futility rule, and the way we did this was as follows.

In the SPRINT study we assessed our patients virtually every two weeks until week 12 and then every four weeks to week 28. So we conducted exploratory analysis using these HCV RNA results included by treatment week, log decline in HCV RNA, detectable/undetectable HCV RNA using lower limit of detection of a lower limit of quantitation, and absolute values of HCV RNA.

The number of patients that had been identified with the treatment week 24 rule was used as our basis. We didn't want to miss anybody who would become an SVR, and we didn't want to leave anybody on therapy who could be taken off earlier.

So we found a number of single time points that were very good negative predictors of response. But we did not find a single time point that would replace treatment week 24. So then we looked for a two-step rule so that a proportion of the patients would come off earlier and the rest of them would come off at week 24.

Could I have slide 1712, please? And this was the stopping rule that we came up with, and this is the basis for how we picked it out. The stopping rule is that if the patient is greater than 100 international units, on the left side of the slide, they're discontinued at week 12; and if they remained detectable at week 24, then they're discontinued.

So the number of patients that would be stopped by the early rule would be 63, which is 9 percent. The additional patients that would be stopped at treatment week 24 would be 50 patients, for a total of 113 patients stopped.

So essentially what this is doing, it's allowing about 50 percent of the patients to be

stopped at treatment week 12 and the remainder of the patients then to be identified and taken off therapy at treatment week 24. And this was the way that we selected the rule.

Now, we looked at multiple iterations around using other criteria, but this was the best rule that we found. The other reason that this rule is somewhat easy for physicians to adopt is that they're used to using treatment week 12 with two-drug therapy to think about stopping therapy in these patients.

DR. CARGILL: Dr. McGovern?

DR. MCGOVERN: I have two separate questions on two different issues. The first question is, did you have adherence data for the lead-in phase on ribavirin and peg? This would help us understand also the point that you made that you tried very hard not to include null responders, and yet about 20 percent of them were null responders.

The second issue is a totally different issue. In terms of safety, did you require EKGs at baseline? And in terms of the deaths, which we

haven't heard characterized, do we have any information on whether anemia was very severe in those patients prior to death? Is there any information about cardiovascular disease?

DR. ALBRECHT: Yes. EKGs were required at baseline, and they were instructed in the protocols, the investigators, to perform analysis sort of cardiovascular monitoring, including EKGs, as clinically indicated. So the investigator was able to do this at any time.

With regard to the deaths, as noted, there were eight deaths in the study, four in each treatment group. Two of the deaths in each treatment group occurred in the follow-up period between 18 and 20 weeks later. Two deaths in each of the groups occurred -- I looked within one week of stopping treatment, because the other ones were very far out. We had one death on boceprevir that was due to cocaine toxicity and the other one that was due to suicide. In the peg/riba alone, we had one suicide and one cardiorespiratory arrest.

With regard to the number of patients that

dropped out in the lead-in, it was about 5 percent among the various treatment groups that dropped out. It was higher in the naive study than in the relapse study. It was about 3 percent in the relapse study and 5 percent in the naive study.

We did not make any decision about the patient's treatment based on the treatment week 4 result. It was a result that was collected, and then retrospectively or as part of our analysis plan, we looked at the effect of treatment week 4 on SVR and other parameters.

DR. MCGOVERN: Well, I just want to know, though, do you have any adherence data on ribavirin during the lead-in?

DR. ALBRECHT: No, we don't have any data on that.

DR. CARGILL: Thank you.

Dr. Murata?

DR. MURATA: I have a clarification request from the sponsor regarding efficacy, using the week 4 log decline in the lead-in phase.

Clearly, the agency has presented data

regarding their analysis on one and half a log viral load decline. Thus, my understanding of the analysis that's been presented early this morning involved week 4 data at less than a log, although in the afternoon, some of the sponsor's slides also included the IDEAL study retrospective analysis using half a log.

Does the sponsor have any additional comments on whether or not one log or half a log may be an appropriate surrogate?

DR. ALBRECHT: I'll let Dr. Gottesdiener further speak about this.

DR. GOTTESDIENER: I don't think it's the sponsor's goal to propose a new definition of null responders for the general worldwide treating population and practitioners. I think the purpose of the FDA bringing forward their 0.5 log drop was to say if you want to address the question of are these people like null responders, this is a little bit more stringent definition. And so they said even with that more stringent definition than the sponsor applied, we applied less than 1 log, the

expected effect of boceprevir is the same.

So I don't think either we or the FDA would really be proposing a new definition of null responders as much as saying these people were essentially comparable to no responders, and, therefore, we can estimate and give a good estimate of what happens with the null responders, as well.

I do want to ask Dr. Poordad if he'd comment on that, because he's one of the people who actually deals with these null responders really on a day-to-day basis.

DR. POORDAD: Thank you.

My name is Fred Poordad. My conflicts are that I do research studies with both Merck and Vertex. I'm an advisor and consultant to both, and I am paid to speak for both. My trip here was funded through Merck.

I do treat a lot of patients and I've been involved in all of these clinical trials, so I do want to make a couple of points that I think are important. One is that while the definition of the 12-week null is an important and useful one, it's

really the issue of interferon non-responsiveness that's more important.

To me, as a clinician, if I can predict earlier who is not going to do well with interferon, it's an important thing. The negative predictive value of the week 12 2-log response is 97 percent. The negative predictive value of the four-week 1-log is 95 percent. In other words, I can predict who is not going to respond at week 4 of week 12 equally.

The concordance is about 90 percent, but it's not trying to say that week 4 and week 12 are synonymous. They're very similar in that you're defining or you're identifying people who are not going to respond to interferon.

Someone asked a very good question earlier. Should we even be treating null responders, people that don't respond well to interferon? And I think that's where the clinician really has to make that decision on a case-by-case basis. Granted, a 30 percent SPR is not great, and we know there are better therapies coming down the road. However,

there are some patients who probably need the therapy earlier. And I think on those cases, the risk-benefit ratio will tell some clinicians that we should treat now.

So I don't think we're trying to cut hairs here with half a log or a log. Please understand that with the PCR technology, there is a half-log variability, and that, in and of itself, could certainly explains some of the discordance that we see. So it's simply a matter of redefining what we've come to think of as 12-week 2-log being paramount. It's really interferon responsive, poorly responsive, or somewhere in between.

DR. CARGILL: Thank you.

Dr. Camardo?

DR. CAMARDO: Thank you. I had actually a couple of questions about the null responders. The first one is -- well, first of all, it seems like that's going to be a lot of the population that is available -- I mean, has hepatitis C. So we can't really exclude them from treatment. And you commented that doctors would want to treat them and

would have to make some decision.

So my question is, would the futility rule apply that we have developed using all of the data from treatment-naive and treatment failures? There's a lot of data there, so we'd have to extrapolate, I suppose, to null responders.

The second question is, is there data that could identify null responders who might have a higher risk to taking the medication or would have some way to identify a patient who may have a benefit to not waiting, because then we could at least put out some guidance about how to at least recognize patients that might be treated.

I don't know exactly who can answer that question.

DR. POORDAD: Let me make sure I understand the question. How do we identify these individuals early?

DR. CAMARDO: Well, how would you -- you commented that there might be some null responders who you should treat if you're a physician, and there are some who may -- you can identify.

DR. POORDAD: Sure.

DR. CAMARDO: Where would you start?

DR. POORDAD: Only speaking for myself, if I know what their fibrosis stage is, that's very useful. A patient who's at stage 0 or stage 1 can certainly wait a few years until we have better therapies for this population. Someone who's a stage 3 or stage 4, who's clearly progressing or has already progressed, then you may feel that a 30 percent likelihood of response is worthwhile.

Someone made the comment earlier that 70 percent of these individuals will develop resistant variants, and this is true, and we don't know what this means down the road; will they be eligible for some other therapy. So I don't think we should rush to treat all interferon non-responsive people, but for individuals where the risk-benefit ratio makes sense, I think we should.

I'd like to also point out there are other studies ongoing where we're trying to find other identifiers early on. I think IL28 is one of them. There are other ones. And we'll certainly continue

to do trials to try and pare down better predictability rules about who we should treat today and who can maybe wait a few more years.

DR. CAMARDO: Thank you.

But what about the futility -- would it apply or would a patient --

DR. POORDAD: Yes. No. Absolutely. I think the futility rule, as you saw there, is very important. You want to have a backup futility as we currently do with peg and ribavirin. We have a 12-week stopping rule today. We also have a 24-week stopping rule. The reason I like the 12 and 24 is it's not a departure from what clinicians already know. If the patient doesn't meet the week 12 futility, they may meet the week 24, and you would not overdose people needlessly.

So, yes, the futility rule would still apply to those individuals.

DR. CAMARDO: Okay. Thank you.

DR. CARGILL: Thank you.

Dr. Clay?

DR. CLAY: I was wondering if the sponsor,

over the break, had any opportunity to look to see the impact on the AKR alleles. When we had talked about the metabolism of the drug split between AKR1C2 and 1C3, that gets you to their inactive metabolites, and then also the other 50 percent that go through the CYP enzyme pathway.

DR. KASSERRA: I'm sorry. Could you clarify the question exactly for me?

DR. CLAY: Yes. I guess when I asked the question earlier today about if you looked to see if there was any impact that this drug had on expression of the alleles, and just in case somebody had some information back in the company and maybe you got it over lunch.

DR. KASSERRA: So we do know that, for example, in blacks, that the diastereomer ratio is very similar to what it is in whites, approximately 2 to 1. We looked at the Phase 3 data. We also know in the different studies that we have done that that diastereomer ratio is not affected by, for example, drug-drug interactions or within the hepatic impaired population.

We have looked at the literature, but there's very little information on the literature in AKR, as I'm sure you're aware. It's a fairly new field. In addition, it's a pluripotent family of enzymes and very ubiquitously distributed. So trying to understand what impact or where the expression might differ could be a challenging type of study.

DR. CLAY: You also included in your materials to us that you had not conducted any p-glycoprotein interactions to date. Is that still accurate from the time you submitted your data?

DR. KASSERRA: That is correct. What I can tell you is that the data we submitted at the time of the filing was limited on P-gp. At the time, we had done a Caco-2 study where we had identified boceprevir as being an inhibitor of P-gp with an IC50 of 25 micromolar. That data was submitted with the filing.

Since then, we've continued to conduct in vitro studies. These data have been submitted to the FDA. They may not, at this time, have been

reviewed by the FDA. I am happy to share that information with you.

We did conduct a further study in MDR. It's a P-gp over-expressing MDCK cells. And in that study, which is more specific and more sensitive than the Caco-2 cells, the IC54 digoxin transport and inhibition thereby by boceprevir had an IC50 greater than 300 micromolar. So we would not expect a direct inhibitory effect of boceprevir on P-gp that would affect other P-gp substrates.

DR. CLAY: Thank you.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: Thanks.

There are a lot of time points that are relevant here where very important measures are taken. And getting back to the issue of the missing data, I wanted to know how far off something would be before it was considered missing.

So, for example, if you want a week 12 measure, probably not everybody had it exactly on

week 12. Some might have had it on week 13 or week 11, and the same with week 24 and the same with the follow-up week 24, the key points.

So I would like to know, how wide was the acceptable window for those measures and what did you do -- you talked about the last observation carried forward, I think, for one of them, but what did you do about the others?

DR. BOPARAI: Navdeep Boparai, statistics. The windows were three-week windows, and it depended on the rigid schedule. Some were tighter two-week windows. The last observation carried forward was just done for the primary efficacy endpoint, and it was just the 12-week was carried forward. But the windows were just plus/minus three-week at the time point.

MR. TRAN: Could you identify yourself, please?

DR. BOPARAI: Navdeep Boparai, statistics.

DR. ELLENBERG: So with regard to the other ones, they weren't counted. I'm sorry. The on-treatment week 12 was carried forward to?

DR. BOPARAI: The follow-up week 12 was carried to follow-up week 24. No on-treatment data was carried forward.

DR. ELLENBERG: So if they didn't have an on-treatment week 12 measurement within three weeks, what happened to that?

DR. BOPARAI: They were counted as failures.

DR. ELLENBERG: They were counted as failures.

DR. BOPARAI: Correct.

DR. CARGILL: Thank you.

Dr. Connick?

DR. CONNICK: This is a question both to the sponsor and to the FDA. I think the implications of the virus -- the resistance mutations are really critical in determining the risk-benefit. I'm curious how you plan to approach that question. I'm also curious if you have tried re-treating anybody with boceprevir who failed, to see if they had the same type of response the second time, one of the people with resistance mutations.

DR. ALBRECHT: We'll talk about the

re-treatment of patients that have failed boceprevir first. No, we have not tried to re-treat any of those patients, and we currently don't have any plans at the moment to do so.

With regard to the development of the RAVs, I think that one of the really important things that we need to remember about these new drugs is that if a patient is cured, that's fine. If the patient fails therapy, based on the data that we showed you, it's highly likely that the patient will develop RAVs, which is why we're using the early futility rules, why Dr. Poordad talked about how he would assess a patient that was a null responder.

So we take this very, very seriously, and I think that physicians will have to think about the options that he has with regard to patients such as null responders before they decide to treat. But, certainly, for many other patients that are highly interferon responsive, the likelihood of having a sustained virologic response is very high, particularly in people that are early responders,

and we're going to use a much earlier futility rule.

DR. CONNICK: How are you planning, though, to look at the clinical significance of it in the future?

DR. ALBRECHT: Dr. Hazuda, do you want to answer that?

We're going to continue to follow these patients, for example. We have them in three-year follow-up. We're looking to see whether they're RAVs decline over time, which we've already shown you that they decline over time. And we're looking to see, over time, whether they go back to wild type, at least by population sequencing, and we're also doing some more extensive work on looking at the RAVs in the follow-up.

DR. CARGILL: Thank you.

Well, we've reached the point in our agenda where we are going to take a 15-minute break. We will leave here now and return promptly at 2:45. And, again, as always, the committee is charged with not discussing this topic outside of this

meeting room.

(Whereupon, a recess was taken.)

Discussion/Questions to the Committee

DR. CARGILL: We are now going to begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

Yes, Dr. Roland?

DR. ROLAND: I just have a process question. I'm wondering how many more people you had on your list with questions.

DR. CARGILL: Because of the time that we need to go through the discussions, we are going to have to terminate the question portion of the session so that we can move forward and provide and answers and guidance as requested by our FDA colleagues.

Here are the questions. The first question, and there are a total of five of them: Please comment on the safety of boceprevir in patients with chronic hepatitis C genotype 1, focusing

mainly on the hematological effects of boceprevir in combination with pegylated interferon and ribavirin.

So we'll now begin that discussion.

DR. SCHECHTER: I think it's clear that there are increased hematologic effects, that is, adverse effects, with boceprevir. But the thing that I would -- my impression is that these have been well managed; that they're reversible, that very serious effects are fairly uncommon, that is, the grade 4, the grade 3 and 4. And the issues of the EPO use, and there does not seem to be any serious effects from the EPO use. But I think to the coming studies or the proposed studies -- I don't know whether there is actually an ongoing study of EPO versus dose reduction -- is going to be a very important one for the guidance of clinicians.

The fortunate thing, also, is that the neutropenia and thrombocytopenia are much less and that the grade 5 complications in neutropenia and thrombocytopenia were pretty uncommon, grade 3 and

4, I meant, and the fact that there didn't appear to be any deaths due to neutropenia or thrombocytopenia.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: I'd like to concur with that view. As a hepatologist, I can say, at least for hepatologists, we've become very comfortable dealing with the anemia issues from peginterferon and ribavirin. So there will be a little more of it, but we can handle it.

I really would like to see a study that compares EPO with dose reduction of ribavirin. I have shied away from using EPO because at least of theoretical concerns about thromboembolism and the case report of aplastic anemia. But with boceprevir coming out and the greater degree of anemia, there may be a greater tendency of physicians to want to go to EPO. So I think that issue ought to be settled.

DR. CARGILL: Thank you. Dr. Clay?

DR. CLAY: I think the data is really clear

that this is a huge advancement in the treatment of hepatitis C and that in the appropriate situation, this drug is going to make huge differences.

But as has been brought up by the members of the committee, as well as the public in attendance, education is going to be absolutely key. And while I would commend Dr. Friedman and the rest of the gastroenterologists and hepatologists here, I think the numbers of people that may begin seeking therapy for hepatitis C are going to increase to the point where they will seek their family physician, their primary care provider, and get treatment from them, and that education across the board, the Katie Couric effect for prostate cancer, if you will, really is going to have to be replicated in order for people to understand not only the importance of the therapy, but the importance of getting proper therapy and adhering to that proper therapy.

I also think special attention needs to be paid to the fact that by people who become anemic or have a drop in hemoglobin responded really is

encouraging the use of EPO, but yet that has not -- there's not approved labeling of use of EPO in this population. And so I would concur with Dr. Friedman that it would be wise to get some quickly assembled data as to some guidelines that could be used for the primary care physicians out there.

DR. CARGILL: Thank you.

Dr. McGovern?

DR. MCGOVERN: In my clinical practice, it's been my usual standard to try to only decrease ribavirin after virologic suppression has been achieved. And so I'm hopeful that with this potent agent, that we're going to get to viral suppression much quicker and that the dose reduction of ribavirin will hopefully be something that is certainly going to be doable and will be safe in terms of bringing hemoglobins to a better level.

One of the things I did notice in the trial was that about 70 patients did not have a change, either a dose reduction or the addition of EPO, even though their hemoglobins were less than 10.

And I'm not sure if we're giving a crossed message that if you're anemic, you have better SVR rates. I think that's just a reflection of better drug exposure, and it doesn't mean that anemia is a good thing and we should be pushing it. But I do think that -- I'm hopeful that when I do back off on ribavirin, it's going to be because most of my patients are suppressed, which is really exciting.

DR. CARGILL: Thank you.

Dr. Ghany?

DR. GHANY: Yes. Thank you.

So my comment also has to pertain to the management of anemia. I guess what I'm going to say is going to partly echo what's already been said. But based on some of the data that were shown by the sponsor, I think on slide 92, that with dose reduction of ribavirin alone, albeit in a small number of patients, the SVR rate is equally as good as patients who are managed with just EPO alone or with a combination of dose reduction plus EPO.

So given the concerns with EPO, including

all the side effects, the cost and the fact that there's been no study that's demonstrated an effect of EPO in increasing the rate of SVR, I would like to suggest that the first approach to management of anemia should be dose reduction of ribavirin, and the use of erythropoietin should be reserved only if the ribavirin dose has to be reduced to a level where it would affect SVR, and I wonder if such data exists, or to preserve the use of boceprevir. Otherwise, I don't see a role for erythropoietin.

The one other point that I wanted to make was that when -- well, let me retract that first sentence. Assuming this drug is approved and is widely available, the concern about anemia is going to be certainly greater, especially for patients with -- the oldest patient with cardiovascular disease. I am concerned about the incidence of angina and MIs in patients with anemia, particularly in the older population and those with co-morbidities, such as diabetes and hypertension.

Thank you.

DR. CARGILL: Dr. Van Dyke?

DR. VAN DYKE: I likewise think that we can probably manage anemia, and I'm particularly reassuring that it resolves so promptly after the therapy is stopped. I think that's a good sign.

I must say I have a little more concern, maybe just theoretically, about the neutropenia. It was relatively common. There were 22 percent with grade 3 and some percent with grade 4, and there were those three events that were life-threatening potentially; I mean, relatively uncommon. But I worry that as we treat more patients, those with co-morbidities, those with other medications, I think we might get into more problems with neutropenia, and I think those are potentially the life-threatening conditions that we need to be more aware of.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I'd like to echo Dr. Ghany's comments. I, too, think that perhaps the use of EPO is not absolutely necessary. We don't have any data that shows that it really does improve SVR

rates.

I'm a little bit concerned about the difference between a magnitude of hemoglobin change and an absolute number. It seems like when we talk about grade 1 through 4, we're looking at numbers as opposed to a magnitude change. I'm not sure; maybe it doesn't matter whether your hemoglobin goes from 18 to 14 as opposed to goes from 12 to 8. But there may be some benefit to a recommendation about monitoring these patients on a regular basis. And I'm not sure whether the magnitude of hemoglobin change is as important as the absolute number.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: I'm assuming that as there's an ongoing study looking at the use of EPO, that the FDA is probably going to wait until they get those results before they say anything about it.

But I will say that I'm glad that the sponsor did do a study that allowed us to see -- have some data with regard to the use of EPO

because it would be inevitable, I think, with this kind of side effect that people will use EPO. So at the very least, we've got some initial data that I think is reasonably reassuring that we're not going to do a whole lot of damage if people use this to treat anemia.

DR. CARGILL: Ms. Dee?

MS. DEE: I'm a little bit more worried than I'm hearing people talk about. I'm not sure what's going to happen when less people get to use EPO. Maybe it won't affect SVR, but I'm wondering if we'll have more cases of anemia and whether they'll be more serious.

I worry about the neutropenia, as well. I think there's a strong signal there that there are issues. And I also wonder about what's going to happen in Peoria when this gets out and people aren't really aware or don't understand -- the best thing Dr. Clay said, when primary care docs start to prescribe this and aren't really aware of the problems or issues that might arise. I really fear for patient safety.

I'm also worried about the idea that -- I mean, I think these things are manageable, but I just wonder if we're going to have some issues. Two or three cases of deaths will set this whole field back a really long way, and that concerns me.

So that being said, I think that it looks like this is manageable. I think that that PROVIDE study, though, I'm really disappointed that that wasn't done way before this, especially since EPO was allowed in this. It would have been very helpful to see the difference between EPO and ribavirin reduction way before this.

I might be mistaken, but I don't think there is any data on what's going on with that yet, so I look very forward to seeing that data when it comes out. But I don't know, I don't think there is any data yet.

DR. CARGILL: Ms. Young?

MS. YOUNG: I just would like to agree with most of the comments that have gone on before in terms of using the reduction, ribavirin reduction versus the EPO, to start with, doing some more

studies on that not only for the sake of the provider and the health care system, but also for the complexity of the treatment for the patient and the side effects. I think adding one more drug is not necessarily the best thing.

DR. CARGILL: Thank you.

Ms. Valbh?

MS. VALBH: I also want to echo some of the thoughts that everybody has talked about today with the use of EPO. Even though it was managed very well in the clinical trial, I think, in practice, we have to understand that there are providers who don't quite follow the guidelines right now for management of ribavirin-induced anemia. And I would like to see tighter controls and guidance on how often CBCs are to be assessed in these patients and more education aimed at the primary care physicians who are prescribing and treating hepatitis C patients.

In addition, even though 40,000 units once a week is used very well in this population, maybe we should talk about weight-based dosing of EPO to

potentially avoid some of the side effects of EPO. We all know the adverse effects of EPO and recently with some of the tighter guidelines on the current indications for it. We don't know if that's going to happen with hepatitis C patients, but if we start using it quite often with hepatitis C patients, we may essentially see the same types of adverse effects. So maybe more of a weight-based dosing versus a standard 40,000 units once a week should be considered.

DR. CARGILL: Thank you. Although I would again remind you that the use of EPO for the treatment of anemia in HCV is an off-label use of the drug and, therefore, I think that's beyond our purview right now.

All right. So I'm going to try and summarize this. It appears that we have reached a consensus on this question, and that is that while there have been several concerns voiced about the hematologic effects which are felt to have been increased with boceprevir, they appear to be mainly manageable; that there are multiple options for

dealing with these, especially if they're, in terms of anemia; first, ribavirin dose reduction and then, if necessary, proceeding from there.

Several have voiced the opinion that this appears to be a great advance in hepatitis C management, but that it's going to be important to have appropriate patient selection. I think we've already heard one answer to one of the questions that's going to be coming up later on, which are several recommendations about dose reduction versus another agent for the management of anemia.

Several of our panel members also pointed out the concerns about neutropenia and what this is going to mean as we go forward and if this drug is indeed approved, what this will look like when larger numbers of people are exposed to this agent, perhaps the experienced may have more profound adverse effects.

But overall, I think what we heard is that the feeling was that these were manageable events, but that there would certainly need to be attention to patient selection was a recurrent theme, as well

as to education of those who are going to use this, as this would be potentially used by individuals who do not have expertise or robust expertise with hepatitis C management in certain populations, as it may be used more by generalists.

Question number 2: Considering the overall potential risks and benefits of boceprevir, do the available data support approval of boceprevir for treatment of patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

I think I'm actually going to go ahead and take -- I'm sorry.

We'll be using the new electronic voting system for this meeting. Each voting member has three voting buttons on your microphone: yes, no and abstain. You might want to take a minute to look at that now and make sure you find them.

Once we begin the vote, please press the button that corresponds to your vote. You'll have approximately 20 seconds to vote. And after everyone has completed their vote, the vote will be

locked in.

After we have our discussion -- I just wanted to give you that information now -- the vote will then be displayed on the screen.

So we're going to go ahead and open question 2 for discussion.

Dr. Roland?

DR. ROLAND: One of the questions I asked that did not get completely answered would potentially have an impact on my evaluation of efficacy. And so I asked the question about loss to follow-up after week 12 and was provided an answer on one of the studies, but not on the other.

If the answer on the other study was similar to the answer on the first study, which was a very small number, sensitivity analysis showed no difference, then I would feel confident.

So it would be helpful just to -- I mean, I'm assuming that FDA reviewers are relatively brilliant and would have picked up if that had been a problem, but I would feel sort of remiss in my responsibility by not confirming that.

DR. ALBRECHT: Do you want me to answer the question?

DR. CARGILL: If you can do it succinctly, yes. Thank you.

DR. ALBRECHT: Yes. This is the RESPOND-2 study and I probably -- we can't put it on the screen maybe, so I'll read it.

There were -- here it is on the screen. This is the same format as the one I showed you. And as you'll note on the bottom, there were no patients in the control, one patient in the arm, two response-guided therapy, and one patient in the boceprevir 48-week therapy that were lost to follow-up and carried forward. So the results in this study, there were even fewer patients than in the SPRINT-2 study.

DR. CARGILL: Thank you.

Dr. Clay?

DR. CLAY: Maybe mine is more procedural than anything else, but in this sentence, as I read it, it doesn't specify the type of chronic hepatitis C infected person, and we're being asked

to vote on it. But then we have subsequent questions in which we're being asked to provide an opinion for various subpopulations of this, but we're not being asked to vote on those.

So I was curious if there was a way to amend this to reflect a particular population or if we were going to take a vote on the subpopulations after the discussion took place.

DR. MURRAY: Well, we usually have one voting question which relates to does this drug make the cut for marketing approval, and I think then picking out certain subpopulations, duration for the subpopulations are more labeling issues, which, when we look at the advice, then we, FDA, looks at kind of the totality of the advice and what was said and take that all into consideration when we actually do the labeling.

So this is just an overall risk-benefit for chronic hepatitis C patients, genotype 1, is it worthy of approval, and then the granular questions will help us with the labels that follow.

DR. CARGILL: Dr. Friedman?

DR. FRIEDMAN: Well, I just have to say, like many people on this panel, I've been taking care of hepatitis C patients for a long time and started out in the business when it was called non-A/non-B hepatitis, and there was no treatment.

Then interferon was approved in 1991, and we were curing, and we didn't use the word "cure," but we had sustained responses in 10 percent. And for the past five or six or seven years, we've been having overall sustained response rates of 45 percent for genotype 1, 55 percent overall. And now, to go to 70 percent really seems like a dream come true for those of us who have been in this field.

There are a lot of problems. This is difficult treatment. So is cancer chemotherapy. But this really, I think, is a major advance. And so I'm very enthusiastic about approving this drug, recognizing that there are a whole host of challenges, including the complexity of the regimens, the cost, and the need for additional data. But if you look at the big picture, I think

this is a remarkable advance over the spectrum of the past 25 to 30 years.

DR. CARGILL: Thank you. I'm actually going to take the chair's prerogative and actually talk about the question, and I would like to echo that and expand it a bit further.

I haven't been taking care of patients quite that long, but I practice in a setting where, unfortunately, approximately 95 percent of our patients are hepatitis C co-infected; 99 percent of that population is African-American.

So, in addition, the difficulties of trying to provide the standard of care for them, going through that standard of care and seeing the outcomes is very often disappointing.

So while I would concur that I have concerns about the complexity of this regimen, I have concerns about people being able to adhere to pill burdens and to some of the other challenges, as well as the hematologic monitoring, which I think will be quite important, I think looking at the faces of a numbers of people who have had poor

options and even poorer outcomes. And to see something like this is truly a chance to say that -- as caregivers, we often advocate and have to provide hope, and it makes you feel like you can come back to the office with some hope.

Ms. Young?

MS. YOUNG: I wanted to ask the FDA. If there is an approval, it's a blanket approval, correct? And then physicians can use it off-label. I guess I'm getting at the question of some of these concerns that we might have about drug-drug interactions and those kinds of questions that might change the standard of care that would be recommended, do we get to go back and look at those or is that something the FDA is going to monitor post-market surveillance?

DR. MURRAY: Well, question 5 allows you to comment on what studies you would like to see. Yes, we will be requesting post-marketing drug-drug interaction studies and then also have a labeling that reflects some of the uncertainties for probably certain drug interactions or probably for

certain 3A metabolized drugs, they'll be recommended not to use. So we are going to be kind of ferreting that out.

DR. CARGILL: Okay. I think at this point, we really are ready to vote. So I would like to just read the charge again before you vote and remind you that do you have the three voting buttons on your microphone, yes, no and abstain. You'll have approximately 20 seconds to vote. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. I will read the vote from the screen into the record. And then next, we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did.

So as this question is now complete and there is no further discussion on this question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have 20 seconds to vote, and

please press the flashing button firmly. If you are unsure of your vote, please press the corresponding button again.

[Voting.]

DR. CARGILL: Okay. You can see the voting results here. There are 18-yes, zero-no, and zero-abstain.

Dr. Knodell, if you could lead us off, please, with your vote and why you voted that way?

DR. KNODELL: Yes. Robert Knodell. I would echo Dr. Friedman's remarks earlier. I think this is a tremendous advance and is going to give a lot of people hope that have already failed treatment once, but are likely to respond to treatment with these new drugs.

DR. CARGILL: Thank you.

DR. KORMAN: Louie Korman. I voted yes, for the same reasons. This is an important advance in treatment. I'm encouraged by the work but concerned about our ability to risk stratify and select patients, which is my misgiving. But that's always my misgiving taking care of patients.

DR. CONNICK: Elizabeth Connick. My vote was yes and for the same reasons. There are risks, but the benefits for the people who do achieve SVR are fantastic. This is a marvelous advance.

MS. VALBH: Pritybala Valbh. I voted yes because this is definitely a much needed advance in the treatment of hepatitis C. And for all those patients who have been on treatment before and who have not responded, this is the answer for them, I think, for the most part. So, therefore, I voted yes.

DR. GHANY: Marc Ghany. I voted yes because I think the data speak for themselves. The efficacy, in my opinion, far outweighs the risks. And I think, actually, this was the easiest part. I think the challenge is now going to be how to use this medication in a broader population and in subpopulations of hepatitis C, who have probably the greatest unmet need and stand to benefit the most from treatment. So I think the easy part is over; the hard work is going to begin.

MS. DEE: Lynda Dee. I would agree with

that assessment. I think that boceprevir performed better in all the arms as opposed to the standard of care. That being said, I'm not sure what to do with everybody in these different categories, as everybody has described, and I think it's my job to be a pain in the neck about those things and to stress patient safety. But as one of my colleagues said at the open mic period, I think this is 21st century advancement, and it's very welcome.

DR. MCGOVERN: My name is Barbara McGovern. I voted yes. I think that this is going to be a real game-changer for our hep C practices, and I can't wait to get back and to talk to my patients about it. I do urge the sponsor to move on with the trials in co-infection because some of my patients are HIV co-infected, and I would very much like to know how to approach that patient subset.

It will also be very important to see how this drug will -- the triple therapy paradigm now will play out in the community.

DR. ROLAND: I'm Michelle Roland, and I voted yes because of the clear incremental benefit

of this drug and the manageable known risks. I have significant concerns about the unknown drug interactions, which I think will have potentially really big implications for the populations in which this drug could be useful and would urge the sponsor to complete those drug interaction studies as quickly as possible.

DR. ELLENBERG: I'm Susan Ellenberg. I voted yes. I'm a biostatistician, so I don't treat patients, but I do look at data, and I think these data show pretty clearly that the risks, while clearly there, as for any effective treatment, they're clearly outweighed by the potential benefits.

DR. CLAY: Patrick Clay, and I voted yes. This drug is going to exponentially improve the outcomes of people infected with hepatitis C. I do have concerns with regard to some of the additional testing that's yet to be completed, but given Merck's history of successful implementation in the community of a three-times-a-day drug and treating a viral infection, I have confidence in them that

they're going to develop what is necessary to make this happen.

DR. CARGILL: I'm Victoria Cargill. I voted yes for three reasons. One, I think it represents a clear advance over what we've had. Secondly, I do agree with Dr. McGovern, I think it changes the game completely and hopefully continues to advance the field. And, third, because I can look into the faces of the people that I have to see on Thursday afternoons and be able to offer them some hope.

DR. STRADER: I'm Doris Strader. I voted yes because I think that the data does show that in patients with hepatitis C genotype 1, there is a very good improvement in sustained virologic response over pegylated interferon and ribavirin alone.

I wanted to emphasize genotype 1 because we seem to be getting very excited as to all patients with hepatitis C, and we can treat with this. And these data were done particularly with patients with genotype 1, so we need to make sure we keep that in mind.

I do have some concerns about some of the other populations that may not have been adequately represented in the studies, but I am sure that we can get to those patients and be able to provide them with care, as well.

DR. VAN DYKE: I'm Russell Van Dyke. I voted yes. I think this drug is going to help eliminate infection from a substantial number of people, and I think that makes it worth dealing with the adverse events, which I think is going to be challenging, but worth it. I look forward to a pediatric formulation and pediatric studies.

DR. GIORDANO: Tom Giordano. I voted yes. Basically, the risks are outweighed by the benefits. I think the risks are not trivial. We do know how to manage these risks, but there's clearly an increase with the experimental medication that is really not explained, and I think there's a lot to learn about how to use these drugs appropriately. But the benefit outweighs the risk at this point.

MS. YOUNG: I'm Kathy Young, and I voted for

approval because I feel that the benefit outweighs the risk and there's a clear need and also to encourage the pharmaceutical companies to develop this kind of novel agent. I think it's important, but at the same time, working on the complexity of the treatment and having agents come down the pike that really would be simpler to use I think is very important with the health system as we are right now moving in toward national health insurance.

DR. SCHECHTER: I'm Geraldine Schechter. And as a hematologist working in a VA hospital, which has about 20 percent incidence of HCV, and my hematologic cancer patients have that incidence and complicate their disease, the benefits really outweigh the risks. And the hepatologists, with some help from hematologists occasionally, will do very well, I think.

DR. FRIEDMAN: I'm Lawrence Friedman. I voted yes for the reasons I outlined previously. I do think you have to be somewhat of a Talmudic scholar to prescribe this drug.

[Laughter.]

DR. FRIEDMAN: But that has a certain appeal to me.

[Laughter.]

DR. MURATA: I'm Yoshi Murata. I voted yes for the favorable risk-benefit profile that was discussed today in support of an approval.

DR. CARGILL: All right. We'll move on to question number 3. Please comment on the strength of the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders, defined as less than 2 log decrease in HCV RNA at 12 weeks during previous course of peg/ribavirin therapy who were not included in the Phase 3 trial P5101 in subjects who had previously failed peg/ribavirin therapy.

Dr. Korman?

DR. KORMAN: This is where the Talmudist in Dr. Friedman is going to come to the fore as he leads us into a pill pull over whether to do this.

My concerns about safety and efficacy and risk stratification really are brought to bear here, because this is the population where, if

we're not correct and we're not careful, we may make these patients, who presumably may be at greater risk for progression -- I don't know that, but maybe -- may cut off an avenue of therapy in advance of newer agents that may be more effective.

So this is of a concern, and I would prefer to see more data and a better understanding of risk stratification.

DR. CARGILL: Thank you.

Dr. McGovern?

DR. MCGOVERN: I think that the FDA analysis with the 0.5 threshold was more convincing to me that what happens at week 4 bears out to week 12. So I thank them for that analysis.

There is no question in my mind that there is a subset of these patients who are poorly interferon responsive that have a good response, about a 30 percent response, and that's real and something I can wrap my head around.

I think that we need to target that, though, towards the patients who really need treatment today in terms of advanced liver disease, because

although there's the 30 percent that are responding, there's the 70 percent who are at risk of viral resistance. In terms of the next wave of protease inhibitors, there are going to be issues of cross-resistance across the next four drugs that are close behind.

So I think I would like to have some direction by the FDA or that we direct the FDA in terms of the labeling that these patients were not explicitly studied and that we are inferring and we are massaging the data. And I just wish that actually they were studied from the get-go, quite frankly, because the caution about not studying them was because we didn't want to give essential monotherapy. And yet we found out that, yes, those patients who are not interferon responsive within that four weeks, they are the ones at risk for resistance. So we did find what they were worried about finding.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I would like to echo some of

Dr. McGovern's comments. I, too, am suspicious of the -- albeit very elegant explanation of how the patients who were initially excluded from study may benefit from this drug, I think that we do know that there are drugs coming along that may be better and hopefully simpler to use. We do know that patients who are cirrhotic or who are null responders may be at increased risk for adverse events. There is some concern about resistance variants showing up in these patients. And I think that in our haste to want to do something, we should probably do no harm.

There was a reason that these patients were excluded initially, and I think that we have to keep that in mind. We do want to do the best we can for the patients who are null responders. And so I think that we owe them the best that we can possibly do. And rather than inference as to how they might do based on some other group, we should really know how they're going to do before we subject them to a very complicated and potentially dangerous -- or increased adverse events.

DR. CARGILL: Thank you.

Dr. Giordano?

DR. GIORDANO: If you actually read the question and take a literal interpretation of the question, the strength of the evidence for use of boceprevir in combination with peg and ribavirin in non-responders, prior non-responders, is zero. There is no evidence. They were excluded from the study. So we're left to extrapolate from data that rely on a number of assumptions and are based on small numbers.

The science of health care has been -- or the science of medicine has been burned many times by making inferences from similar but not exactly the identical population that you're trying to treat. So I would say a strict interpretation is there is no evidence and a more generous interpretation is the evidence is weak to moderate, at best.

DR. CARGILL: Thank you.

Dr. Ghany?

DR. GHANY: Yes. Actually, Dr. Giordano

basically stole my thunder. That was how I was going to answer this question. But if you read the question literally, the evidence, in fact, doesn't exist. It still concerns me why the sponsor chose to not include these patients and then later come back and try to get an indication for this particular subgroup of patients.

I think if we stretch the data and say that there is some data that the drug is efficacious in null responders, we really have to be careful. And I think I agree with Dr. Poordad that if you're going to consider treating a null responder, you really need to individualize therapy for each patient, because we can do harm, particularly if these patients develop antiviral resistance. There really isn't a lot of data on what the re-treatment of these patients will be with other agents, and we may be doing them more harm than good.

So I think that is something that we all need to be cognizant of. There are going to be better treatments coming down the road. And particularly for individuals with mild disease, I

would strongly suggest that they wait and not be treated and certainly wait until we have more information about treatment in larger groups of patients who are null responders.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: So I wish a study had been done in which these patients were included prospectively, but that wasn't the case. I'm a clinician, not a scientist, so you were able to convince me that about 30 percent of these patients will respond.

What's happened is we've built up a reservoir of non-responders to peginterferon and ribavirin, and they are waiting in the wings for the next generation of drugs to come along. And probably some of them can continue to wait, but some of them can't, and we're going to want to use them on some of these patients. It's going to be selective, and it's going to be the people who have advanced fibrosis. We're going to be concerned about resistance and an increased risk of side

effects, but we're also going to be concerned that we're running out of time.

So I personally would like to see this indication for the drug, but I'd like to see it used very selectively.

DR. CARGILL: Thank you.

Dr. Knodell?

DR. KNODELL: I would like to again echo what Dr. Friedman has to say. I will accept these data. I think that they took people who had failed dual treatment and put them in a study, and 30 percent of them responded.

I'm looking at these old milestones in therapy of chronic hepatitis C, and, I mean, we got pretty excited when we got a 6 percent response with interferon, and then 16 percent response treating, and then we added ribavirin and we got 34 percent.

So we're talking about a response rate that certainly is 1 out of 3. And I would echo, again, you're not going to treat people with stage 1 fibrosis or a G1S1 Ludwig score. You're looking to

treat these people with G3S4 or some of those folks where you see a very active hepatitis problem. You're not going to treat null responders with minimal disease.

Again, you have your futility barriers in place, a 12-week and a 24-week, and I think the incidence of variants is not real high in these short treatment periods, and I think it's unlikely that you're going to remove these people from further therapy, therapeutic considerations.

DR. CARGILL: Thank you.

Dr. Clay?

DR. CLAY: First off, I always get concerned when you hear that there are future things coming, because you never know -- I guess you don't know what you don't know. But one of the things that we can't control is should this drug get approved, who is going to use it and in what population. But what can be controlled, if that's the correct word, is if this drug is supplied, then that individual is enrolled into a data registry; that the elements of data that are captured would be that ideal to

answer the questions of these experts around the table where you are simultaneously providing a drug to a patient that desperately needs it, even though the formal studies have not been done. But over time, we may gather enough information that we are able to make better decisions moving forward while the more rigorous structured trials are being conducted and/or other potential agents are brought to market.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: The ideal data -- I mean, that seemed like torture the data until it confesses to me. I'm just not convinced by that at all.

The 30 percent of people, they were really small numbers. And I didn't get to ask this question, but on page 12 of the sponsor's briefing document, it says that in vitro after 15 days, there was a 2 log drop of RNA with this drug.

So I wonder -- I know that hepatitis resistance develops quickly, and I would think that resistance to this would develop quickly no matter

what the futility rules are. And that might mean that patients are resistant to boceprevir and cross-resistant to other HCV BIs.

I guess the question is how badly does a patient need it, and, again, I'm going to agree with Dr. Clay. In what population should we think about this?

I mean, these people were not in the trial, and I think that the label should really clearly state that they were not included. I don't know. This is going to be a long label, is all I can say.

[Laughter.]

DR. CARGILL: Dr. Ellenberg?

DR. ELLENBERG: I guess I'm more leaning toward the side of those who see the arguments that were made by both the FDA and the sponsor that, in fact, these patients were represented in the studies, and that I'm prepared to accept that it's more likely than not that there will be approximately a 30 percent response rate.

Whether that's enough to treat a patient seems to me like a very individualized decision,

and I would not like to tie hands of clinicians if I felt that this, in fact, will have a substantial response rate, to tie the hands of physicians who think it's appropriate to use in some cases.

I understand the cautions that people have raised. I'm not exactly sure what would be put in the label to help that out. But it seems to me -- I'm ready to believe that there is a response rate in these that's sufficient that it ought to be available to this patient population.

DR. CARGILL: Thank you.

Ms. Young?

MS. YOUNG: I guess I am leaning more towards the prior null responders not being included because the evidence wasn't there. Also, I think it's very important that this drug be used prudently to start with, so the risk stratification idea is something I'd support. And it would be nice to have a trial or a launch that was successful, and I think proving success in the groups that really would meet a risk stratification first and then maybe considering it for the other

ones that are a little more questionable would be one way to go.

DR. CARGILL: Well, this is going to be a little bit more challenging to summarize, because it seems our consensus really splits down into a fork in the road.

We've certainly heard that there are concerns being raised about potential safety issues for null responders in addition to what potential other outcomes could happen to them; for example, not only just not responding, but perhaps closing future options, the development of viral resistance.

We've heard from people who are hepatologists on the panel that they are comfortable with the notion that they could still treat null responders, for several reasons, not the least of which is that one would take into account individualized therapy; that, secondly, one would also take into account the clinical picture of the patient so that the therapy can be individualized, being offered mainly to those individuals who are

clearly ill as opposed to those who could perhaps afford to wait.

Finally, we heard some suggestion that perhaps some of the futility rules would be of assistance in this regard.

But we also still did hear a minority opinion of those who felt that this was a patient population that should not be treated in this way or should be treated with extreme caution and perhaps even the offer of a registry, so that in exchange for being able to treat a patient that falls into this category, that there would be the opportunity to capture data so that we could learn something about this patient population.

So I think we've seen that the committee remains as divided as it was at the outset of the discussion in this particular area.

Yes, Debra?

DR. BIRNKRANT: Given that we have all of this expertise here, I was wondering if I could ask if this were formally studied, is there an SVR rate below which you wouldn't feel comfortable using?

Everyone is mentioning the 30 percent response rate. Is there a rate that if you had studied this formally, you would not be comfortable with using?

DR. CARGILL: Dr. Knodell?

DR. KNODELL: I'm going to sidestep this. The question is difficult to answer because it depends on how sick the patient is. You get somebody who is really -- the data is clear. If you get a sustained response rate in somebody who has cirrhosis, you absolutely cut their rate of hepatocellular carcinoma almost down to nothing.

So when you've got that kind of clear-cut result that you can get clinically, you're willing to take a 1 in 5, 1 in 6 or 7 probably. If you get down in the low 10 percents, the low double figures, then you've got to ask yourself whether the benefit outweighs the risks. But, boy, once you get up in the 20 percent and certainly in 30 or 40 percent rate, when you start thinking of what you can accomplish by an SVR, it's really pretty great.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: I think that's right. I think that if you're going to exclude it from the label, then I think that's more important. But if you're not, as somebody said before, years ago, they were happy with 5 or 6. So I think it's up to the patient to decide whether they're willing to take a risk. I just would like to know what the data is and what the evidence is. So after that, I think I would like to talk to my doctor about whether it works for me.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Actually, because of the known benefits of SVR, I think that the more relevant question is what is the acceptable risk that we're willing to take, and for that I don't think we have any data.

So I don't think I can answer that question, because if you ask a hundred hepatologists, you're going to get a different number from everyone.

DR. CARGILL: Did you want to continue to

hear comments, Dr. Birnkrant, or did you get the answer you needed?

DR. BIRNKRANT: I think I got the answer, for the most part.

DR. CARGILL: Dr. Clay?

DR. CLAY: I think the answer to your question would come from the registry. Over time you're going to see people's response rates. And then over time, you will be able to see what has been accepted and what has not been accepted. And the experts in the field, in conferences when that data is presented, they're going to begin to hone down which population it is over time. But it is an individualized basis until we have data to show us it's not going to be done.

DR. BIRNKRANT: Do you think the futility rule should be different for this population then, because we're concerned about functional monotherapy perhaps?

DR. CLAY: Time will tell. I'm sorry, we don't have the data here.

DR. CARGILL: Dr. Van Dyke, do you want to

have the last word on this?

DR. VAN DYKE: Well, I'm going to skirt the question, as well, but it seems to me the downside is resistance, principally. So I think what we don't know is, A, does resistance persist, for how long. This isn't HIV where you've got pro-viral resistance there forever. So maybe if you wait long enough, the resistance goes away.

I personally don't know how much cross-resistance there might be with some of the other agents then in development, but that would be an important issue, as well, because if there are different resistance patterns, then I think you might be more willing to take the risk of developing resistance if you -- even a 30 or 40 percent response I think would be great in these people that currently have no response at all.

DR. CARGILL: All right. So we'll go on to our fourth question. As you can see form the screen, it's fairly complex, so we'll break it up into pieces; speaking about Talmudic scholars.

Please comment on the strength of the

evidence to support response-guided therapy with boceprevir in combination with pegylated interferon and ribavirin.

Should certain groups of patients receive longer durations of boceprevir plus peg/ribavirin therapy than that evaluated in the response-guided therapy arms?

So let's start with that, and then we'll go through the questions targeting, first, treatment-naive. But let's start with that.

Ms. Dee?

MS. DEE: All right. I'll go. Again, they were small numbers, and I remember Dr. Ellenberg's question about whether that was real or just an affect. But it also appeared to me that patients that stopped boceprevir after a certain period of time, that's when they had virologic failure. So it would seem to me that keeping on boceprevir longer as opposed to a longer course of peg/riba would make more sense, especially given the anemia considerations. And the duration of anemia might be an important factor. I think that's an

important factor to consider.

It seems like the agency and the sponsor have agreed on this, so I guess we still answer it, though, right?

DR. MURRAY: Well, we put two options down for you to consider for duration, a full duration -- I guess when we get to talk about certain groups, A, 44 or 32, or you could suggest your own, I guess. But I don't think we came to any firm agreement because we wanted to hear what you had to say.

MS. DEE: I think the 32 might be sufficient. The triple therapy might be better than longer, than 20 weeks of PR.

DR. CARGILL: Dr. Roland?

DR. ROLAND: I find this a very vexing issue, and I actually wish I had one table that showed all of the response rates across the three arms and then in the important subpopulations.

The reason it's such a hard issue to address, it's not hard to address when the response-guided therapy rate was higher than the

other rate, but when it's lower, the study was not designed to compare the two active arms. And so we have absolutely no idea what that means.

So then I kind of wonder, well, then does it become another one of these individualized decisions where, for some patients, it's going to be more important to have the absolute best chance of an SVR, and for others, they are more than willing to take a little bit of risk, that maybe this isn't quite as effective and they're going to have a shorter duration of therapy. And without a head-to-head study of the two active approaches, I don't know how else to think about it.

DR. CARGILL: Dr. Ghany?

DR. GHANY: Actually, I agree completely with Dr. Roland that the studies were not designed to answer these particular questions. And what we're trying to do is do subgroup analysis on smaller cohorts of patients, and I think we're stepping on shaky ground here if we're going to use this as a labeling indication.

I think one of the last questions put

forward to the panel is what other additional studies are needed, and these are clearly studies that need to be designed to answer these important questions.

Thank you.

DR. CARGILL: Thank you.

Dr. Knodell?

DR. KNODELL: I don't know where that 32-week treatment came from, but it seems to me that you've got data that if you have a late responder, the only thing we have data on is a full 44 weeks of boceprevir, of triple therapy, and I don't know how you can possibly ignore that and shy away from it in terms of your labeling.

You've either got people who respond very quickly, and they can be treated for the 28 weeks or you've got people that are slow responders, and the only thing you have any data on is a full 44 weeks of triple treatment.

DR. CARGILL: Dr. Connick?

DR. CONNICK: I agree with what everybody else has already said. I think without real data,

a study that truly addressed this question, we're simply guessing.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: So, again, I speak as a clinician, not as a scientist. The first thing I'd say is I'm glad we don't have to vote and we don't have to make this decision, because it's complicated. But my advice to the people who do have to make the decision is there clearly is a lack of complete data. And what clinicians are looking for is something that's simple and easy to remember and not complicated, and that's good for adherence for patients, too. And I think those factors have to be taken into account. Despite the appeal of Talmudic scholarship, I'd actually rather keep it in my head if I could.

So I like the idea of response-guided therapy. Clearly, it's going to have a role. There are some people, the early responders, naive patients who are going to be able to come off therapy sooner. But when you get into all these

subgroups, if it gets too complicated, we're going to be shooting ourselves in the foot. People are not going to be following it, following the protocols precisely, and patients are not going to be adhering precisely. So I'd consider that in the decision-making.

DR. CARGILL: Thank you.

Dr. Ellenberg?

DR. ELLENBERG: I agree with most of what has been said. I'm not so worried about not giving very specific directions to people. I think there is a place for individual patient values in these things, and I the data that are here, I think it may help clinicians make decisions about somebody who's really, really miserable on the therapy but is in the category that looked like they did pretty well with a shorter course to help make the decision that maybe it's okay to go off earlier and to maybe push harder for people who are doing pretty well on the therapy and they were in the category that maybe they would do better.

But I agree that we really don't have the

kind of data that we would need to make a very strong recommendation one way or the other.

DR. CARGILL: Dr. Strader?

DR. STRADER: I will agree with some of those comments. Two things, in particular. I tend to be a purist. There is a reason that we require that studies be done and they be done in a certain fashion. There's a reason we're all sitting here around this table to discuss these.

So I think that we should try to focus on the data that we have. It's nice to be able to make some inferences because we do want to take care of patients who have not been included in the studies, but it's important to realize there's a reason that we use the scientific method.

Again, to echo Dr. Friedman's comments, putting on my gastroenterology hat for a second, there have been some studies that show that people are more likely to comply with colonoscopy screening if the recommendations are simple. You give people five or six different methods that they can choose to be screened and it's much more

difficult for people to make a decision as to what to do as opposed to giving people very clear recommendations that say this is the preferred thing that we do. So I think that we should really try to keep that in mind when we're making these labels.

DR. CARGILL: Well, with that, we're going to go on to the A part of the question, which is looking specifically at treatment-naive patients with detectable HCV RNA at week 8 and undetectable at week 24, or otherwise known as late responders; again, the strength of the evidence to support response-guided therapy and should certain groups receive longer durations of boceprevir.

Dr. McGovern?

DR. MCGOVERN: I think the bridging analysis that the FDA did was interesting and provocative. I would like to see a study to really sort that out. So I think this is an area that would require more patients.

DR. CARGILL: Thank you.

DR. MURRAY: May I ask -- I mean, if the

answer is we need more studies and it's interesting, does that mean the default is basically arm 3 and not response-guided, not shorter therapy?

DR. CARGILL: Dr. Roland?

DR. ROLAND: So I'm trying to draw my table that I was looking for. I think what I'm seeing in the naive study is that in the two arms in the early responders, they are the same, 97/96. So how could you argue against response-guided therapy in that group? In the late responders, there is a potential difference in the direction we don't like, so 66 for the response-guided therapy and 75 for the long therapy.

I would be much more uncomfortable -- actually recommending response-guided therapy in late responders would not feel comfortable to me, given that.

DR. CARGILL: Dr. Ghany?

DR. GHANY: I think to answer your question, Dr. Murray, the answer is yes. And I agree with what's just been said. In the absence of other

data and from the small sub-analyses suggesting that even with a small dataset, that longer data gives you better SVR rates, that that's the only recommendation that you can come to at this point.

DR. CARGILL: Dr. Clay?

DR. CLAY: In the label, which is what I think we're sort of talking about here, it could be structured such that it is approved for use for this duration of time and you actually give the range for that, and that consideration can be given to discontinue this if you see this at this time point. I mean, that's more of a guideline statement, though, than what we actually would find in FDA labeling, because there's so many contingencies there.

I think that's what you're looking for here, but I don't exactly know how to help you write the wording for the package insert.

DR. CARGILL: Dr. Knodell?

DR. KNODELL: I guess my previous remarks I thought were already dealing with section A here. But I would point out that over the years, we seem

to have made a mistake on the short side duration of treatment. We initially recommended interferon for six months; then we went to 12 months. We initially recommended interferon and ribavirin for six months; then we went to 12 months. Now we're treating some people who are slow responders who don't have a negative RNA at 12 weeks but do show a 2 log increase; and, then, our negative at 24 weeks, we're carrying them out to 72 weeks.

I'd hate to take one step forward and two back by stopping treating people early, assuming -- I mean, again, you have clinical considerations like how well they're tolerating the treatment. But I think that if we've got a situation where it looks like there is a difference between a little longer treatment duration and a higher sustained viral response, we should take that.

DR. CARGILL: Ms. Valbh?

MS. VALBH: I'm going to agree with that. These patients are typically harder to treat anyway, and I don't think that a shorter duration

of treatment in this population is going to show that much more benefit. I think that they do deserve a longer duration of treatment. And then going back to what Dr. Friedman said, we have to keep in mind that within the labeling, we don't want too many variations of all these subpopulations. We need to be very clear and not have dosing recommendations or treatment recommendations that are not going to be easy to remember or practiced and out there.

DR. CARGILL: Dr. Van Dyke?

DR. VAN DYKE: I guess neither of these comments are very rigorous, but, first of all, to me, it makes sense that if someone is a slow responder, they need to be treated longer. I apologize for that, because that's an emotional statement, but it makes sense to me.

Looking at the data and going beyond what we can really conclude from it, that table was already quoted in the treatment-naive that for the late responders, you went from 66 to 75 percent response by going to the longer duration of therapy, 48

weeks.

That difference is not seen in the same table looking at the previously treated group. Granted, it's 32 weeks, not 28 weeks in the response-guided therapy. So it's a little bit longer, and in that group, it's the same, 79 and 72 percent, almost the same; in fact, better for the response-guided therapy.

So I guess what I'm saying is if you want to believe that longer therapy is better, I think you can get a suggestion that for the treatment-naive, there is a hint, a trend maybe, a trend that longer therapy was better and that with longer therapy in the previously treated ones, already, you didn't see that difference.

DR. CARGILL: Dr. Ellenberg?

DR. ELLENBERG: I can understand that somebody treating patients and looking at these data might feel like they might want to treat those late responders longer, but looking at the data themselves, the difference is so slight, it's not even close to a statistically significant

difference. And, again, given that you've got -- in the other study, there really is no difference and there is no difference in the early responders.

It's very hard for -- I don't see how we could make any kind of a strong statement that the shorter therapy is clearly to be avoided in these late responders. It's something that might be worried about. There are other medical areas where we gave more treatment, and it turned out that less treatment was just as good, and you avoided problems.

So, again, I'm not comfortable recommending a strong recommendation that people have the longer course. I think people can look at the data. But I don't know from these data that the shorter isn't just as good, and it certainly has some advantages.

DR. CARGILL: Dr. Ghany?

DR. GHANY: In the spirit of keeping things simple, I tend to agree with the comments that we should just have sort of one regimen for these individuals. I wonder if the FDA even has to

address this particular subgroup and whether this could be left for the practice guidelines to discuss some of these nuances of treatment.

Would you like to comment on that?

DR. MURRAY: Well, I guess we don't necessarily need to get that nuanced in the label, but if there are subgroups where you definitely would not go with shorter treatment, I mean, we'd certainly like to hear that. I mean, if you do feel strongly about a certain group, and I guess we'd be talking about cirrhosis in B, we'd certainly like that.

I guess we certainly can wordsmith the label so that there is freedom for individualized therapy and treatment duration depending on the patient situation.

DR. GHANY: The reality is that the physician taking care of the patient is going to make these decisions on whether to shorten the course of treatment or extend it for the recommended duration based on tolerance. So the labelings are really guidelines, and it's really a

decision between the physician and the patient.

DR. CARGILL: Thank you.

Ms. Dee?

MS. DEE: I don't want to be inconsistent about what I said about the null responders and no evidence being there, but I did see there was a difference -- excuse me. There seemed to be better SVR rates with the triple therapy.

I'm a cancer survivor, and I was supposed to get nine treatments, and at eight, I was half dead and my doctor said, "Good enough, girl." So if you have patients -- maybe without cirrhosis, let's just put that qualification in there -- that you're seeing at a certain point in time you don't think are going to make it through, it may be a judgment call between you and that patient. But if it's not in the label that this might be efficacious, then the doc might not even try it.

I mean, the idea that we should make this more simple is like a joke at this point. It's not simple in any way, shape or form. So if we could make it better for patients -- I mean, all of those

extra weeks of interferon is a horror show, and I think that's getting as real as I can get. So if we have any evidence that that, in fact, might not be necessary, I think we ought to share that.

DR. CARGILL: Dr. Korman?

DR. KORMAN: Not being a scientist either, I was just looking at the numbers, and not being a statistician, and these numbers are two patients either way and they're equivalent. I also treat these patients. Sixteen weeks of longer therapy is really difficult, and we know that these regimens are a little bit more toxic than the other regimens.

So I don't know how you wordsmith this, but if you give somebody a pass at 32 weeks because they're doing okay, then that seems to me to be a perfectly acceptable way to phrase the guideline so that clinicians are not obligated to treat for a full course of therapy.

DR. CARGILL: Thank you.

Well, as if that isn't complicated enough, we'll revisit our favorite group of null

responders. And I feel like I'm a drowning man going down for the third time, but I'll stick in here.

Does the panel want to give any additional advice to the FDA regarding null responders?

I'm sorry. Let's look at blacks and those with advanced fibrosis or cirrhosis.

Dr. Clay?

DR. CLAY: I'll say it, but I guess you probably already talked to Merck about this. How are you going to better describe predicted response in that population? What is unique? What is different about that population that resulted in this response rate? And I don't have any crystal ball for you on that one.

DR. CARGILL: Ms. Dee?

MS. DEE: I think the cirrhosis area is much more clear than the case for African-Americans, blacks, whatever.

I really just think that you need to say that the numbers were small or this is what happened with certain people or a certain amount of

people and let docs decide what they want to do with their patients. I just don't feel comfortable that there were -- I mean, it seemed like there were a lot more cirrhosis cases in that one arm, if I recall, and that that obviously needs longer treatment. I think that's pretty clear. But I'm not as clear about what to do with, for instance, late responders who were black.

DR. CARGILL: Thank you.

Dr. Ghany?

DR. GHANY: I would agree with what Ms. Dee said. The case is a little clearer for patients with advanced fibrosis or cirrhosis. The data does suggest that these patients would benefit from a longer duration of treatment -- well, a standard course of 48 weeks of therapy. But, again, the numbers are small. There are only 9 percent of patients with this in the naive trial.

I'm sort of on the fence with what to do with African-Americans. If you believe that some of the difference can be explained by cirrhosis, I think that only explained 50 percent of the

difference. It doesn't explain all the difference. So I'm not certain how to respond to this, whether they do as well with response-guided therapy as with the 48-week course of treatment.

DR. CARGILL: Dr. Strader?

DR. STRADER: I agree that the cirrhotic patients, it seems like an easier decision to make. I'm looking at the sponsor's slide 32, and it appears -- and it pains me to say so -- that when I look at the p-values -- when we looked at response-guided therapy for blacks, the p-value was .044, so we're just getting there, as opposed to when we talk about 48 weeks, it's .004.

So it appears, even with these small numbers, that African-American patients probably do better with the full 48 weeks of treatment as opposed to the response-guided therapy. I would be a little bit more encouraged if the response-guided therapy p-value was a little bit lower. But, again, it's hard to say, but these are the data that we have.

DR. CARGILL: Ms. Young?

MS. YOUNG: Obviously, it's cost-benefit of covering your bases versus exposing that population to increased risk. So with the data we have, do you feel it's strong enough to go one way or another? I mean, are you leaning toward the --

DR. STRADER: As a clinician, I would probably tell my black patients I think it's better to do the full 48 weeks, because I find that if you ask the patient a question, this came up on the other side of the table, "Do you want to take another 16 or 24 weeks of treatment and be reasonably assured you're going to get a good response or do you want to cut it short and it may work, it may not, but if it doesn't, we're going to have to do this all over again," people will say, "I'll do the full 48. I don't want to take the chance that it may not work and I have to do it again."

So speaking personally, I would probably tell my patients, based on the data that I have here, my African-American patients, let's do the full 48.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: This is almost a question for Dr. Ellenberg, not being a statistician. But I'm wondering, with this sort of unusual trial design, where we've got two comparisons, whether a multivariate analysis that includes black/non-black as a predictor, that includes fibrosis as a predictor, and includes treatment as a predictor could help us to understand what the variables are that are impacting the response.

DR. ELLENBERG: I think the answer to that is maybe. The numbers here are quite small, so it might be more helpful. Again, I'm looking at that 42 percent versus 53 percent, remembering that that 42 percent was somewhat lower because of people who dropped out before they even got the drug.

I think what Dr. Strader said is a perfectly reasonable approach to one's patients, but I think the data are just not strong enough for us to say this is the way everybody should treat their patients.

I remember that the FDA asked us -- did express some concern about that 9 percentage point difference, but it's 22 out of 47 versus 29 out of 55. It's just a very unstable estimate.

DR. CARGILL: Dr. Knodell?

DR. KNODELL: Along these lines, I'm just curious. When Merck set this study up -- I address this to the sponsor.

When you were treating treatment-naive people, you did a four-week lead-in and then 24 weeks of triple therapy. And then when you do your study design for the non-responders, you do a four-week lead-in and 28 weeks of treatment. Now, you obviously must have thought that this is a particularly tough group of people to deal with and that maybe a longer treatment period is reasonable.

If you could comment on what made you make that decision, it may help us with our decision as to how long we should be treating these people.

DR. CARGILL: Yes. Thank you.

If the sponsor address that question.

DR. GOTTESDIENER: Yes. I'd like to address

it and also point out that the analysis that was requested for the multivariate analysis we have done. And if you give us one minute, we can actually share that with you about blacks.

So it's important to realize how this late responder/early responder works. The way it happens is treatment week 8, people are either detectable or non-detectable, and if they make it through to the point at which the actual decision is made, which is week 28, they either stop therapy at that point or if they're a late responder, they go on additionally. And what we're really talking about is what is the duration of boceprevir treatment in those individual patients.

So in practice, what we did in our trials is we said if you look like you're responding early, you should stop. If you look like you're responding late, you should get more. It really follows a very simple idea as one goes forward.

What we did find is -- and as the FDA pointed out -- is that if you try to understand, in fact -- if you looked at some of those late

responders and you asked how much boceprevir they need, could we stop that at 24 weeks or go on farther, in practice, there was a small difference there.

What the sponsor really thinks is it's very clear that there's a difference between 24 and 48 weeks. The hard decision is where between those two time points to stop the boceprevir therapy. So one way to look at it would be to say we studied 24 and 48, 48 was better, and that settles the issue.

I think what we and the FDA have done is we've said that isn't the only data we actually have. We also have data from the treatment failure patients, and when we look at those same type of patients in treatment failure patients, they look exactly the same between those two groups. So from our looking at the data, we would say, clearly, a bit more than 24 weeks is important, but the treatment failure patients tell us 32 weeks is enough.

Now, having said that, the important

question is can we actually tease out in the blacks what we should actually do there. And Dr. Koch, who is a professor of statistics, may be able to explain the multivariate analysis and help the committee understand why we think blacks should get, in fact, the ability to have RGT.

DR. KOCH: I'll be very quick. Gary Koch, biostatistics department, University of North Carolina, a statistical consultant to Merck.

As Dr. Albrecht pointed out, there were more patients in the 48-week regimen who actually showed a good response at week 4, and she then showed what the mITT analysis did when you accounted for that. But there also were more patients in the week 48 analysis -- I'm sorry -- in the 48-week group who had undetectable virus at week 8, 12, 16, 20, 24, and this is with both arms receiving the same treatment through the 28-week period.

So there was a random tendency for the 48-week group to have more favorable status prior to 28 weeks among the blacks than in the response-guided treatment. When multivariate analyses were

recently done to remove that random advantage, then these groups then became very close together, and actually there's an adjusted difference of about 2 percent in the all black ITT or mITT population.

I could show a slide that revealed some of that, but basically if you do a multivariate analysis that adjusts out all the random imbalances that favor the 48-week group at all weeks prior to week 28, that difference shrinks.

DR. KNODELL: You didn't address my question. The question was, your response-guided treatment for the people that hadn't responded before is 28 weeks, whereas your naive treatment period with triple drugs before you make a response-guided decision was 24.

Why that four-week difference before you made a decision?

DR. GOTTESDIENER: Actually, I'm not quite sure that that's factually correct the way you're describing it. In one study, there were four weeks of lead-in and 24 weeks of therapy, triple therapy, and that was week 28.

DR. KNODELL: That's naive.

DR. GOTTESDIENER: That's correct.

DR. KNODELL: (Off microphone.)

DR. GOTTESDIENER: I see.

Jan, do you want to go ahead and answer that question? What you're really asking is why was the branch point for RGT 28 weeks in one study and 36 weeks in the other.

DR. KNODELL: Yes.

DR. ALBRECHT: The longer therapy for the response-guided therapy arm in the non-responder study was based on observational data that we made in an earlier study where we saw that patients that were very poorly responsive needed at least 24 to 28 weeks of therapy after they became negative.

So using that data, we said in non-responder patients, that for the response-guided therapy arm, that we would make the duration of therapy longer. And so we used four weeks of lead-in plus 32 weeks of boceprevir and then added on the 12 weeks of two-drug therapy.

So that data that supported that was from an

early dose finding study that we did.

DR. CARGILL: All right. I'm not sure that I can summarize all --

[Laughter.]

DR. CARGILL: -- of that for my FDA colleagues. But I think that there are several points that have emerged from this. One is that we heard from the panel that it seemed that some of these questions could almost be jumping off points for additional studies that they would want to consider, and we will talk about that in our next question.

Another is that it appears that from some of the data reviewed by the sponsor, that some of these differences at the -- for blacks, it appears, really are a function of the analysis, and if I understand you correctly, they were the same all the way along.

The third point is I think we're still back to where we started, I hate to say, with our null responders in that we're still hearing a certain amount of discomfort around a firm recommendation

with some expression of opinion that people should be free to be able to make the decisions that indeed we don't want to err on the side of being too short and others saying that we don't feel that we have the information.

I think that's probably the best I can do from such a fairly complicated discussion.

Our last question is, in addition to pediatric studies, are there other post-marketing studies you would recommend to further define risks or optimal use of boceprevir in clinical practice?

I think given the many conversations that have gone on from the table, especially from my hepatology colleagues, I think this is a place where you can jump in with robustness and certainly list a number of things that you would like to see. So please have at it.

Ms. Dee?

MS. DEE: I'm going to leave the efficacy studies out, because I think that everybody else can comment on them. But I'm really interested in the drug-drug interaction studies. I'm amazed.

I'm shocked that we don't have more information on antidepressants given the depression that occurs with interferon.

Methadone, that's shocking to me that that hasn't been done already; the HIV protease inhibitors. It's just very disappointing that this stuff hasn't been done. And I heard today that they're going to be done, but I just need to say that I know that there's race in all of these drugs, but I think it's irresponsible that these studies haven't been done before now, and I hope they get done post haste.

The other thing that worried me was the anti-diabetic studies. And I think there was one more thing. The contraceptives, the combined oral contraceptives. I mean, come on, we want women in these studies, and we want other populations. I mean, we really need to get this work done.

I should have said this probably the last time around, but there are not a lot of blacks in these studies, and we have all these really complicated issues. Why aren't there more blacks

in these studies? We need to do Phase 4 studies with just blacks like we did in HIV for GRACE and Latinos. I just don't see what -- I don't know what it's going to take for the sponsors to learn that they need to do this now or they're going to have to do it later, because I just really think that it's important, especially in HCV, to have these efficacy and safety questions answered in black people.

I was very impressed with the slides that the doc from the VA Administration showed. I'm sorry, I don't remember her name. But they are the real people that have hepatitis C. So we really need to get all of this information so that the real world can benefit from these 21st century advances.

DR. CARGILL: Thank you.

For the record, that's Dr. Belperio. And I'm going to actually jump the line and list my own requests of studies.

One of the things that I am quite concerned about is that our patients often are very eager to

have these options, but I think it's like anything else; when you begin to take them, you realize the devil is in the details. And so having a feel for the adherence, the impact on adherence, which we always know changes after we get into broader populations, is really going to be quite important.

In addition to the impact on adherence, what are the types of support that can help with adherence, because clearly this is going to be critical? We offer people an opportunity to have another shot at SVR, but, again, there are other mitigating factors. And, particularly, a regimen is going to require lots of pills, has other side effects. I think that's going to be something we'd want to know about.

So I apologize to my colleagues for jumping the line, but I think after sweating through four questions, I could do it.

Dr. Clay?

DR. CLAY: I just want to echo some of the drug interactions that really I think are important. Obviously, conducting a study in women

of childbearing potential on a variety of oral contraceptives is key because this disease is pervasive throughout the entire population.

The lack of data on antidepressants is concerning given the fact that that is something that is used quite frequently in this population at the outset of therapy for hepatitis C, as well as the over-the-counter and complementary medicines that were mentioned earlier today by the members of the public, specifically milk thistle. And you do have some data that's been provided about the likelihood of interactions with methadone and buprenorphine, as well as other medicines.

These are studies that are very easily done, very rapidly done in normal healthies, and you can provide an answer probably before this drug would need to be in the pharmacy shelves. So I think this is certainly a list of trials that could be conducted.

One thing that is not drug interaction-related, and you may already have an answer to this -- and, if so, that's great, and I apologize

for missing it -- would be if your data initially showed that you didn't have anemia reported in your normal healthy volunteer studies, and I'm not aware that normal healthy volunteer studies generally run for four weeks at a time. And if, indeed, you did four weeks' worth of normal healthy studies and you didn't see anemia, that's great, but if not, then I'd like to see that.

Thank you.

DR. CARGILL: Dr. Roland?

DR. ROLAND: So for the record, I'd like to echo my support of all of what's been said so far. And following up on your request around adherence and supports for adherence, I think a very well thought out series of demonstration effectiveness studies are going to be really important for clinical guidance; obviously, very different from efficacy studies.

I'm also really interested in the use of this drug in the post-transplant context. And so there's a series of steps that need to be considered for that; obviously, the interactions

with the immunosuppressants and then all of the tolerability issues in the post-transplant setting when people are on all kinds of myelosuppressive agents.

It seems like it would be pretty simple to do a virology study that looks at the ability of the triple therapy to re-suppress the virus in people who had resistance that then reverted to wild type. That wouldn't have to be an efficacy study, but that would give us some reassurance about whether there's antiviral activity.

This is a little bit more of a question. I'm not sure if it's important to study this drug in the hepatitis B and C co-infected patients. Maybe some of the hepatologists have some thoughts about that.

DR. CARGILL: Do any of our hepatologists want to address Dr. Roland's question?

[No response.]

DR. CARGILL: While we're thinking, Dr. Ghany?

DR. GHANY: Well, again, I also agree with

everything that's been said. And I'd also like to add a few other suggestions for post-marketing studies.

Of course, we need to study this drug in all the special populations, so the post-transplant is an obvious one, larger populations of African-Americans, larger populations of cirrhotics, those with psychiatric issues and dependence issues.

The final suggestion I had is in an effort to try to simplify this regimen, I'd like to see studies where there is no lead-in phase, because it's not clear to me that a lead-in phase is actually essential for this regimen. And that's a study that could be done very -- that's an easy study to do.

DR. CARGILL: Thank you.

Dr. Strader?

DR. STRADER: I agree with that last one, Dr. Ghany. I think that that point is well taken, that there is not -- it may be that we don't need a lead-in phase.

I think maybe resistance studies might be

interesting just to know. The sponsor said that there doesn't appear to be any effect of baseline variants on SVR, but it may be interesting to know are they talking about the duration that variants remain positive and is there some cross-resistance that may affect your ability to respond to others.

We also talked about EPO versus ribavirin dose reduction in patients. Is there a minimum dose of ribavirin below which we think we should not, with the triple drug therapy, be going and where EPO might be used.

DR. CARGILL: Thank you.

Dr. Friedman?

DR. FRIEDMAN: I just felt shamed into commenting on the hepatitis B and C issue. It's a little complicated. Peginterferon, of course, can be used to treat hepatitis B. So you can do studies in patients who have combined infection, co-infection with B and C using this regimen to see what happens. But then I think if there is a response to C, but not to B, then you want to know about the interaction between boceprevir and the

nucleoside and nucleotide analogue alternatives for the treatment of B. So you'd want to know something about those drug interactions.

DR. CARGILL: Dr. Knodell?

DR. KNODELL: Just a little expansion on Dr. Friedman's. Generally, when you have dual infection, one or the other of the viruses is the primary virus, and you can kind of look at either your HBV DNA or your hepatitis C RNA, and you'll generally see one will be high and one will be low. And I usually treat the one that's predominant. Generally, it seems like you don't have a dual infection with both viruses blasting the liver.

My one comment on the additional studies. There hasn't been many -- there isn't much data on people over 65 who, one, will have some different levels of drug metabolism, and we're getting more aggressive, I think, in treating older people now with hepatitis C, particularly because of some data that was reported at the last liver meetings about the high rate of hepatoma that develops in people with hepatitis C over 65.

So, again, it shouldn't be real hard to accumulate some data along those lines and see whether or not older people have a similar clinical response as your earlier treatment studies.

DR. CARGILL: Thank you.

Dr. McGovern?

DR. MCGOVERN: If I remember the Kohl paper correctly, SPRINT-1 didn't show a major difference in efficacy whether you had a lead-in phase or not, but there definitely was a difference in terms of the incidence of resistance.

So, again, it's getting back to is resistance important, and it keeps getting back to will wild type return for good. If you re-expose the patient to that drug, will those RAVs return? And we don't know that.

I guess in terms of how that bodes to additional studies, I guess it would be nice if we do have data that these are not detected by population sequencing, maybe the sponsor could consider also looking at deep ultrasequencing, pyrosequencing.

DR. CARGILL: Thank you.

Dr. Clay?

DR. CLAY: When you conducted your response-guided therapy, did you re-measure drug concentration at the point where they were failing?

I didn't see a lot of heads nod that time.

The last couple of questions that I was asking, it was like, "Oh, yeah, we did that."

Why didn't you do that? That, to me, is a key thing to this. I mean, adherence is key. We've talked about adherence, and we've talked about the daily diaries. I run a Phase 1 through 4 research center. I'm aware of how to manipulate those patient diaries, because we generally incentivize our patients to complete the diary.

But if you did not reassess the plasma concentrations, and, ideally, to make sure that the drug is getting where it needs to be, at the time of failure, I guess I would like to see that being done in some fashion.

DR. CARGILL: Thank you.

Ms. Valbh?

MS. VALBH: I am very disappointed in the drug interaction studies and the lack of the studies, especially with oral contraceptives and with the antidepressants. And I would like to comment on what Dr. Clay said earlier, that maybe those studies are quicker to do and we could do those before the product hits the pharmacy shelves.

In addition, and this is maybe later on down the road, even though there is good treatment right now for other genotypes -- I know we're looking at genotype 1, but there is a subset of patients who do not respond, like genotype 2 and 3 that do not respond to standard of care. I would like to see studies done on the non-responders for the other genotypes to see if this product will increase their chance of an SVR.

DR. CARGILL: Thank you.

Dr. Connick?

DR. CONNICK: I wanted to echo some of the statements previously made. I think what Dr. Roland suggested, re-treating people with boceprevir who failed but whose resistance

mutations have disappeared is absolutely key to address the significance of the resistance. And that study could probably be done pretty soon.

In addition, I think adherence is extremely important and undervalued, and if we could figure out ways to perhaps improve adherence early on, maybe push more people into being early responders, if that is possible, that might be incredibly cost-effective rather than treating them longer.

I also think we have another drug that may get approved and a nice head-to-head study might be warranted with that drug, if it gets approved.

Lastly, I think we should start thinking about treatment trials for people who have failed boceprevir and are there ways that we can enhance those people's responses, giving them more interferon or ribavirin or what. Thanks.

DR. CARGILL: Thank you.

Dr. Giordano?

DR. GIORDANO: I guess I have to go on the record and say I think there needs to be a study in null responders because I don't think that's

actually been stated in response to this question yet.

Similarly, I think it would be useful to have a study of different treatment durations in late responders. I think that question is not answered, and it would be useful to have that answered, in addition to supporting actually everything else that everyone else said.

DR. CARGILL: Thank you.

Dr. Roland?

DR. ROLAND: I'm wondering if people with bleeding disorders were included in this study and, also, if they're being included in the HIV co-infection study.

[No audible response.]

DR. ROLAND: Neither? So I certainly heard from public comments that that's an important population to understand what the -- especially the risks.

DR. CARGILL: Thank you.

Dr. Van Dyke?

DR. VAN DYKE: I think it would be

worthwhile doing a study looking at the IL28B genotype up front, because it may well be that people with the CC genotype need shorter duration of therapy. So I think if you could define that, I think that would allow us to sort of customize therapy for individual genotypes.

DR. CARGILL: And, Ms. Young?

MS. YOUNG: I agree with everything that -- all the suggestions that have been made, and particularly the VA presentation had some very good suggestions about the drug-drug interactions and adherence and risk stratification in terms of the regimen and dosage and resistance.

I'm not sure how you prioritize, because I know there's a cost to all of this, but maybe looking at the profile of the target population and figuring out what's most relevant to that, as well as the side effect issues that we're concerned about.

DR. CARGILL: Well, compared to question 4, we have over 37 studies that have been recommended for our sponsors. So, obviously, you all are going

to be gainfully employed for a long time. Just to revisit some of them, the drug-drug interaction studies alone, we'd all be as old as Methuselah getting through all them. But they would include everything from certainly our HIV medications, antidepressants, which I certainly echo. We've heard about other agents, such as milk thistle, certainly buprenorphine and methadone.

Populations, specific, special populations, and in that group I would include both racial and ethnic minority populations, such as African-Americans and Latinos, as well as individuals who have diseases that place them in special populations, including those with bleeding diatheses or those who are null responders, cirrhotics, those who are co-infected with hepatitis B and hepatitis C.

In addition to that, a population of individuals who are post-transplant and may become infected both in terms of the tolerability of the drugs, interactions with their immunosuppressives. Certainly taking a look at do we need a lead-in

period, and, if so, what does that look like and why.

Sequencing, a very important point made about people over 65, who especially, what I would concur, the more recent data on hepatoma in this population. Data on non-responders from other genotypes and what does that mean. Re-treatment with boceprevir after treatment failure and the viral resistance mutations have disappeared.

So this is just the beginning of a very long list of some very important studies addressed in the questions that I think, again, point out that we can have robust efficacy trials, but as we've all learned in basic statistics 101, there is no perfect study. And so we have to always keep taking repeated bites at the apple.

So I think at this point, I'm going to ask the division to give us their last words, being our resident, Talmudic scholars, I guess.

DR. MURRAY: I don't know if we have any final words, unless Dr. Birnkrant does. But we do want to thank the committee for bearing through all

of the complex presentations and doing everything they had to do get here. And we really appreciate your taking time out of your busy schedules to help us wrestle with some of these questions. We appreciate it a whole lot.

Adjournment

DR. CARGILL: Well, I will thank you from the chair, thank you to the sponsor, thank you to the FDA, certainly thank the participants, and also for the public who has come in to hear these. And we are now adjourned.

(Whereupon, at 4:40 p.m., the meeting was adjourned.)