DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC)

Tuesday, August 6, 2002

8:00 a.m.

Holiday Inn Bethesda
Versailles Ballroom
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Roy M. Gulick, M.D., M.P.H. Chair
Tara P. Turner, Pharm.D., Executive Secretary

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Victor G. DeGruttola, Sc.D.
Janet A. Englund, M.D.
Courtney V. Fletcher, Pharm.D.
Princy N. Kumar, M.D.
Wm. Christopher Mathews, M.D.
Jonathan M. Schapiro, M.D.
Sharilyn K. Stanley, M.D.
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CONSULTANTS (VOTING)
F. Blaine Hollinger, M.D.
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CONSULTANT (NON-VOTING) PENDING NEW AVAC MEMBER
Kenneth E. Sherman, M.D., Ph.D.

INDUSTRY REPRESENTATIVE (NON-VOTING)
Eugene Sun, M.D.

PATIENT REPRESENTATIVE (NON-VOTING)
Brett Grodeck

FDA
Mark Goldberger, M.D., M.P.H.
Debra Birnkrant, M.D.
Rafia Bhore, Ph.D.
Katherine A. Laessing, M.D.
Tan T. Nguyen, M.D., Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GULICK: Good morning, everybody. I am Trip Gulick from Cornell. I am pleased to call to order this meeting of the Antiviral Advisory Committee.

I would like to welcome the members of the committee, the sponsor, where it only feels like it is 5:00 a.m. California time, and a special welcome to the audience. My high school drama teacher would be very distressed that I have my back to you all day, and so do some members of the committee, but we can see the slides better that way, so we will give that a shot.

I would like to start with introduction of the committee, so if the members of the committee could please state their name and their affiliation, and we will start with Dr. Sun over on the righthand side.

Introduction of Committee

DR. SUN: Eugene Sun, Abbott Laboratories.

MR. GRODECK: I am Brett Grodeck, Patient Advocate.

DR. WOOD: Lauren Wood, NCI.

DR. KUMAR: Princy Kumar, Georgetown

University.

DR. SCHAPIRO: Jonathan Schapiro, Stanford.

DR. SO: Sam So, Stanford.

DR. LONDON: Tom London, Fox Chase Cancer Center.

DR. ENGLUND: Janet Englund, University of Washington, Seattle.

DR. STANLEY: Sharilyn Stanley, Texas Department of Health.

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

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

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

DR. HOLLINGER: Blaine Hollinger, Baylor College of Medicine in Houston.

DR. SJOGREN: Maria Sjogren, Walter Reed Army Medical Center.

DR. SHERMAN: Ken Sherman, University of Cincinnati.

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

DR. WONG: Brian Wong, the VA Hospital in

West Haven and Yale University.

DR. NGUYEN: Tan Nguyen, Medical Officer, FDA.

DR. BHORE: Rafia Bhore, FDA.

DR. LAESSING: Kay Laessing, Medical Team Leader, FDA.

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

DR. GOLDBERGER: Mark Goldberger from the Office of Drug Evaluation IV, FDA.

DR. GULICK: Thank you, everybody.

Tara Turner will now read the Conflict of Interest Statement.

Conflict of Interest Statement

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this

meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to the following participants: Dr. Victor DeGruttola for his consulting for a competing firm on unrelated matters for which he receives less than $10,000 a year, and for a federal grant to his employer for studies involving the product at issue. The grant is greater than $300,000 per year.

Dr. Jonathan Schapiro for his consulting for a university on unrelated matters. The university receives funding from two competing firms and the co-marketer of the product at issue. He receives between $10,001 and $50,000. And for his consulting for a competing firm on unrelated matters, he receives between $10,001 and $50,000.

Dr. Princy Kumar for ownership of stock in a competitor and co-marketer, valued between $5,001 and $25,000.

In addition, a limited waiver has been granted to Dr. Kenneth Sherman for a federally funded contract to his employer which involves competing products and the product at issue. The funding received is greater than $300,000 per year.

A copy of the waiver statements may be

obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. Brett Grodeck, a patient representative, would like to disclose that he owns a nominal amount of stock in Gilead. Eugene Sun has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

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

DR. GULICK: Thanks very much.

Dr. Kopp, just for the record, could we have you state your name and your affiliation, please.

DR. KOPP: My name is Jeffrey Kopp. I am with NIDDK Intramural Program.

DR. GULICK: Thanks very much.

We will now turn to Dr. Birnkrant who will have some introductory remarks on behalf of the Division.

Opening Remarks

Debra B. Birnkrant, M.D.

DR. BIRNKRANT: Good morning. I would also like to welcome everyone to today's Advisory Committee meeting. Specifically, I would like to welcome all of our Advisory Committee members, consultants, guests, and representatives of Gilead Pharmaceuticals to the first day of a two-day meeting related to drug development for chronic hepatitis B patients.

The first day will be devoted to a review of the safety and efficacy data contained in the New Drug Application for adefovir dipivoxil for the treatment of chronic hepatitis B.

[Slide.]

With regards to the second day, we will be

discussing clinical trial issues and, as a preview, we will be discussing the following points with our Advisory Committee experts.

Given that we have recently received multiple new protocols for new drugs asking specific questions of us, and we thought at this public meeting we would be able to address some of the issues and be able to advise sponsors based on the advice we receive.

So, as a preview to tomorrow, we will be discussing some of the following points related to clinical drug development for chronic hepatitis B. We will be discussing endpoints for both compensated and decompensated patients, the patient populations for study, selection of controls and duration of trials and long-term follow-up.

With regard to the endpoints, we will be discussing virologic, histologic, serologic, and biochemical endpoints.

With regard to patient populations for study, we will be discussing issues related to E-antigen-positive and negative subjects, as well as those coinfected with HIV.

With regard to controls, we will be discussing and asking our experts to comment on the

need for placebo-controlled trials versus active-controlled trials, and with regard to duration of trials and long-term follow-up, we will be asking pointed questions related to that given that the long-term sequelae that we are trying to prevent, namely, hepatocellular carcinoma and cirrhosis, are events that take place much into the future, after clinical trials have been completed.

[Slide.]

As an introduction to today's meeting, briefly, chronic hepatitis B affects between 350 and 400 million subjects worldwide and 1.25 million subjects in the United States. Globally, it is the most common cause of cirrhosis and hepatocellular carcinoma.

To date, there are limited treatment options both in scope and number. Alpha-interferon was approved in the early 1990s. It is limited by its side effect profile and the patient population for which it is indicated.

Lamivudine was approved in the late 1990s for chronic hepatitis B. It is limited by the development of resistance with resistance occurring at about 20 percent the first year and up to 50 percent by the fourth year in both

E-antigen-positive and negative subjects. So, clearly, there is a need for new treatments for chronic hepatitis B patients.

[Slide.]

Now, adefovir dipivoxil is not new to this Advisory Committee. We presented the New Drug Application for adefovir dipivoxil for the treatment of HIV back in 1999. At that time, higher doses of adefovir were studied in support of the HIV indication, namely, 60 mg and 120 mg. However, nephrotoxicity was seen with these higher doses and occurred after 20 weeks of treatment.

As you recall, the nephrotoxicity was manifested by an increase in creatinine, phosphate and bicarbonate wasting, proteinuria and glycosuria, and at that time, both the committee and the agency determined that the risk-benefit profile of adefovir dipivoxil for HIV was not acceptable.

I would like to commend, however, Gilead Pharmaceuticals for having the foresight for developing lower doses of this drug product, this promising drug product, for the treatment of chronic hepatitis B patients.

[Slide.]

Today, you will be hearing about the principal studies contained in the New Drug Application. Trials 437, 438, and 435. The three principal trials, 437 and 438, were placebo-controlled in E-antigen-positive and negative patients, and examined lower doses of adefovir, 10 mg and 30 mg.

Trial 435 was an uncontrolled clinical trial that was conducted in patients who were post-transplant or on the waiting list for liver transplant, and the majority of those patients were lamivudine-resistant.

In these clinical trials, lower doses of adefovir dipivoxil were studied, and the applicant has chosen 10 mg as the to-be-marketed dose because it provides a balance between safety and efficacy for these patients.

Minimal nephrotoxicity was seen with the 10 mg dose in Trials 437 and 438, and some nephrotoxicity was seen in patients in 435, but you have to keep in mind that those patients in Trial 435--and this will be brought out by the FDA presentation--were advanced patients receiving nephrotoxicity agents, such as immunosuppressant drugs.

[Slide.]

Turning now to the endpoints in the clinical trials, the primary endpoint was histologic improvement defined as greater than or equal to a 2 point decrease in the Knodell necroinflammatory score without worsening fibrosis at 48 weeks.

Secondary endpoints included virologic, biochemical, serologic, and they were a reduction of HBV DNA, ALT normalization, and loss of e antigen with or without seroconversion in Trial 437.

[Slide.]

Today, we will be asking our Advisory Committee to comment on the safety and efficacy contained in the New Drug Application for adefovir dipivoxil, and during our question period in the afternoon, we will specifically be asking our Advisory Committee to comment on the use of adefovir in both compensated and decompensated liver disease in the setting of lamivudine resistance, in the setting of presumed precore mutant disease, and in patients with comorbidities.

In addition, we will be asking the committee to comment on the applicant's resistance

program to date and any future resistance surveillance plans, and we will be asking the committee to comment on postmarketing studies.

[Slide.]

With regard to our agenda for today, following my comments, Gilead will make their presentation, which will be led off by Dr. Zach Goodman. This will be followed by a break, and FDA will present, specifically, Dr. Rafia Bhore and Dr. Tan Nguyen will make the FDA presentation.

This will be followed by a period for questions and clarification. Following lunch, there will be an Open Public Hearing with further committee discussion following the Open Public Hearing, and questions will be posed to our Advisory Committee, and then the committee will adjourn.

Thank you very much.

DR. GULICK: Thanks, Dr. Birnkrant.

I would like to turn now to the sponsor, Gilead Sciences, for their presentation to the committee.

Sponsor Presentation: Gilead Sciences, Inc.

Introductory Remarks

Alan Taylor, Ph.D.

DR. TAYLOR: Good morning. I am Alan Taylor, Vice President for Regulatory Affairs at Gilead Sciences.

[Slide.]

We are happy to be here today to present the results of our development program for adefovir dipivoxil in the treatment of chronic hepatitis B.

Our presentation today will demonstrate that adefovir dipivoxil administered as one, 10-mg tablet daily is a safe and effective therapy for chronic hepatitis B.

[Slide.]

The results will support our proposed indication that adefovir dipivoxil is indicated for the treatment of chronic hepatitis B in adults with evidence of active liver disease.

[Slide.]

Joining us today are: Dr. Jules Dienstag from the Massachusetts General Hospital, Dr. Zachary Goodman from the Armed Forces Institute of Pathology, Dr. Paul Klotman from the Mt. Sinai School of Medicine, Dr. Eugene Schiff from the University of Miami School of Medicine, and Dr. Teresa Wright from the University of California, San Francisco.

[Slide.]

Today's presentation will begin with a presentation by Dr. Zachary Goodman, who is the Chief of Hepatic Pathology at the Armed Forces Institute of Pathology. The title of his presentation is Evaluation of Liver Histology in Clinical Trials for Chronic Hepatitis B.

Evaluation of Liver Histology in Clinical Trials for Chronic Viral Hepatitis

Zachary D. Goodman, M.D., Ph.D

DR. GOODMAN: Thank you, Dr. Taylor, and good morning, everyone.

[Slide.]

This morning you will be hearing about the efficacy of adefovir for treatment of chronic hepatitis B. As you have heard, histologic improvement in the liver biopsies is the primary efficacy endpoint.

So, as the pathologist who looked at the slides for the study, and I am also the pathologist who has been involved in other studies including drugs that have been presented for approval, we thought it appropriate that I give you an introduction explaining what it is that we look for in liver biopsies when we were doing an evaluation

in the clinical trial for treatment of chronic hepatitis and explain how that if a drug really works, we can tell by looking at the liver biopsies.

[Slide.]

Now, let me refresh your memories about what we presume to be the pathogenesis of the liver damage in chronic viral hepatitis. The hepatitis viruses, as you know, are not directly cytopathic, but the viruses do replicate in the tissue, and there is a host immune response to the viruses, and it is the combination of viral replication and the host immune response that causes tissue damage.

The tissue damage then can lead to scarring, and when the scarring is bad enough, that becomes cirrhosis, and some patients with cirrhosis will develop hepatocellular carcinoma.

The death of the patient occurs because of a combination of processes, but it is either as complications of cirrhosis or hepatocellular carcinoma, or a combination of the two, but as you know, this takes decades to evolve, so as a surrogate for the clinical endpoint, which is death of the patient, we can use histologic evaluation of the liver biopsies.

We can look at the tissue damage, look at the scarring, look at cirrhosis if it's present, look at carcinoma if it's present, and have a snapshot of where the patient is in this process and surmise what we think will be the future course based on where he is at the present time.

[Slide.]

So, how we do this? Well, we look at the histologic features of hepatitis, and these have been very well characterized over the past number of decades. Both acute and chronic hepatitis share histologic features, but in different proportions. There is hepatocellular injury, which we recognize by seeing apoptosis of liver cells, lesions that we refer to as focal necrosis.

There is inflammation which can be in the parenchyma or in the portal areas or the periportal areas, and then there is regeneration and repair of the issue and sometimes scarring in chronic disease. So, let me show you some examples of these.

[Slide.]

Over on the left is a liver call which is in the process of apoptosis. Its cytoplasm is very eosinophilic, it has been fragmented, and there are

some lymphocytes that are associated with this dying liver cell. That is how liver cells die in hepatitis is through the process of apoptosis.

Now, cells that undergo apoptosis disappear from the tissue very quickly and often what we are left with is a cluster of inflammatory cells showing where apoptosis occurred. That is a lesion that we traditionally call focal necrosis.

[Slide.]

That is what happens in the parenchyma. In chronic hepatitis, there is lots of chronic inflammation in the portal areas. Over on the left here are two portal areas in a liver biopsy from a patient with chronic hepatitis.

The portal areas fill up with lymphocytes. That is one lesion, that is the chronic portal inflammation, but a more important lesion is what is present at the periphery, in the periportal area right at the interface between the portal connective tissue and the surrounding parenchyma.

That is where we see a lesion that has traditionally been called piecemeal necrosis, or a more modern term for it is interface hepatitis. This is shown at higher magnification here, right at the edge you see cells like this.

This is a liver cell which is surrounded by cytotoxic T-cells that are causing the liver cell to undergo apoptosis, and the T-cells are also pushing against adjacent liver cells which will also soon be damaged.

Now, that is an important lesion because that is what leads to scarring, to fibrosis, and to evaluate fibrosis, we need to stain for connective tissue, and the one that is most often used is the Masson trichrome, which is shown, here, which stains collagen this nice blue color.

Now, in the normal liver, there is very little collagen present, just a little bit around the vascular structures. This is a liver biopsy from a patient who has had quite a bit of scarring. It is not at the point of cirrhosis yet, but all the blue is scar tissue. Blue is bad.

[Slide.]

So, in the context of a clinical trial, how do we go about doing histologic grading and staging, which will give us some sort of meaningful evaluation, and it is important to keep in mind the goal is that we want to assess whether there is improvement in a cohort of patients who are receiving a new form of therapy in comparison to

some sort of controlled cohort that is a group of patients receiving placebo or a comparator.

[Slide.]

So, how do we go about doing this? Well, there are a number of ways it can be done. The major method that we use is a semi-quantitative numerical scoring. That is what has been done in all of the previous studies, and it is being done in the one that we are discussing today. I will go into that in a little more detail in a second. We can also do a ranked assessment of the biopsies, which I will talk about in a few minutes.

In I think just about every study that has ever been done, there has been one pathologist looking at all the slides to minimize variation in the way the slides are scored, and we get paired biopsies from each patient.

That is, we have a pre-treatment biopsy and a post-treatment biopsy, but the pathologist is blinded as to which treatment the patient is receiving, which treatment arm he is in, and the order of the biopsies, don't know which one is pre-treatment or post-treatment.

[Slide.]

Now, the semi-quantitative numerical score

that has been used the most is referred to as the Histology Activity Index or the Knodell score, and that is the oldest one that has been around. It has been used in the previous studies, and that is the primary endpoint in the current study.

What the pathologist does in doing this sort of scoring is to look at the different components of the injury, look at the periportal injury, that is, the piecemeal necrosis or interface hepatitis. Confluent necrosis, I didn't mention, and the periportal injury, of course, gets scored on a scale that goes from zero to 4.

Confluent necrosis, I didn't mention before, but that refers to bridging necrosis or multilobular necrosis, which is actually quite rare in chronic viral hepatitis, but once in a while it is present and you can get some extra points for that.

The parenchymal injury refers to the apoptosis and the focal necrosis. That gets graded on a scale of zero to 4, and the portal inflammation also gets graded on a scale of zero to 4, and then we can total them up to get a grade for the inflammation, an overall score, which is the grade of the disease, which theoretically can go

from zero to 18. We will also look at the stage of the fibrosis, which I will come back to in a minute.

[Slide.]

Let me show you how we go about doing this though. We start with the periportal injury, and I will show it first in cartoon form. This is the interface hepatitis with the piecemeal necrosis. That is the lesion that you recall leads to fibrosis.

Now, the green circles here represent portal areas and the black blobs are lymphocytes in the portal areas. Now, we are not really concentrating on the portal inflammation itself, but what happens right at the interface, the periportal area where the portal connective tissue meets the parenchyma.

If there is a little bit of information there, the lymphocytes in contact with liver cells, then, we would grade it as mild. If it is more than a little bit, but less than 50 percent of the circumference, then, we would call it moderate, and if it is more than 50 percent of the circumference that is involved, we call it marked.

There is a number associated with each of

these. Mild gets you 1 point, moderate gets 3 points, and marked gets 4 points. Notice there is no 2 there because as this scoring system was originally conceived, it was meant to be a weighted score. The authors thought that moderate was more important than mild, so they gave it greater weight.

[Slide.]

Here are some real pictures from liver biopsies. The two at the top are both mild, and it is not the inflammation again, but the inflammation tends to correlate with the amount of interface hepatitis. We just have a little bit here and a little bit over there. Those would both be considered mild.

Here is a portal area down here that has no interface hepatitis here, but it has got some here, got some here, got some here, a little less than 50 percent of the circumference, so we call that moderate, and the one over in the lower right has interface hepatitis all the way around, more than 50 percent, so we would call that marked.

But, of course, all four of these portal areas could be from the same liver biopsy, so the pathologist has to do a mental average to come up

with an overall score. So, that is the periportal injury.

The parenchymal injury, we do similarly. I will only show that in cartoon form. The red blobs are apoptotic bodies, liver cells undergoing apoptosis, and the little black things are clusters of lymphocytes.

If there are only a few, it is moderate, if there are many of them, it is marked, and everything in between in moderate.

[Slide.]

The same is true with portal inflammation. If only a few portal areas have--here again, the green is portal areas--if only a few of them have lymphocytes in them, that is mild, if all of the portal areas are stuffed with lymphocytes, that is marked, and everything in between is moderate, and we get numbers associated with each of these categories.

[Slide.]

So, we look at all there various things, add them up, and come up with a score for inflammation, which can go from zero to 18. Then, we also have to do the fibrosis, which can go from zero to 4.

Now, in some of your documents you will see, and on some of the slides you will see what is referred to as the total Knodell score. As this score was originally conceived in the 1970s, the stage was added into the overall score, so it was both the grade and the stage were added together. That is what is referred to as the total Knodell score.

But in every study that has been done, the fibrosis has been separated out from the inflammation because the fibrosis is not expected to change very quickly, whereas, the inflammation may. So, we have a Knodell inflammatory score, which is zero to 18, or a total Knodell score, which goes from zero to 22.

[Slide.]

Let me talk about the fibrosis a little bit now. We are changing colors here, so that the portal areas are blue, because remember in the Masson stain they are blue. Normal portal areas, which would be these, are very small, difficult to see without a special stain. If we had no fibrosis, that gets a score of zero.

Almost everybody who has chronic hepatitis has some fibrosis in the portal areas. They

enlarge, some of them remain round in contour, some of them develop spikes. That is portal fibrosis, and gets you a score of 1.

In people with progressive liver disease, the fibrosis begins to extend between adjacent vascular structures and portal areas, and you get bridging fibrosis, which would be a score of 3, and when that gets bad enough, you have complete nodules forming or cirrhosis, which is a score of 4.

[Slide.]

There are three biopsies from patients who are in the adefovir study, three needle biopsies. This one on the left only has portal fibrosis around the portal areas, the one in the middle has bridging fibrosis, and the one on the right has complete nodules even though some of them are cut across, that's cirrhosis.

[Slide.]

I am going to digress for just a minute and talk a little bit more about fibrosis scoring because some of the FDA documents and some of the other slides that you will see refer to what is called the Ishak score. I want to tell you where that came from.

Ishak, you can see the name there, that is my colleague, Kamal Ishak, at the AFIP. He was the pathologist who worked with Knodell on the original Histologic Activity Index, so the Knodell score is actually an Ishak score.

But this was a scoring system that was designed in the late 1970s before we knew quite as much about the natural history of liver disease as we do now. They didn't think that fibrosis would change very much, so they didn't pay a great deal of attention to it.

Over here on the left you can see the degrees of fibrosis. Portal fibrosis in the Knodell gets a score of 1, bridging fibrosis, no matter how many bridges, gets a score of 3, and cirrhosis, whether it is early or late, gets a score of 4.

By the early 1990s, there was interest in looking with a little bit more detail at fibrosis, and a group in France, a group of pathologists who call themselves the Metavir Group came up with their own scoring system for inflammation and fibrosis, which has been used quite a bit in some papers published from Europe in looking at fibrosis.

The only difference between their scoring system, though, and the original Knodell, is that they added a 2, so if there are a few bridges you get a score of 2, and many bridges you get a score of 3.

Then, Ishak and some other European colleagues in the mid-1990s decided to refine the original Histologic Activity Index. Ishak was the first author on it. They has come to be called the Ishak score.

They made a few minor changes in the way inflammation is graded, which hasn't been used very much, but they I think they made a major advance in evaluation of fibrosis. They came up with a six-stage scoring system for fibrosis, which actually gives you enough range to see changes in the course of studies.

So, if there a little bit of portal fibrosis, you get a score of 1, a lot of portal fibrosis a score of 2, a few bridges 3, many bridges 4, incomplete cirrhosis 5, and established cirrhosis or advanced cirrhosis 6.

In the FDA document, they mention some analyses that were done using the Ishak score. In the course of doing the study, I did both the

Knodell score and the Ishak score, the Knodell score is the primary endpoint, but the data is available for the Ishak score and can be used for other subsequent studies. So, that is where that comes from if you have any questions on that.

[Slide.]

So, what do we know then about histologic evaluation? Well, the grade of inflammation, that is, the activity, the HAI inflammatory score tends to correlate with the ALT levels although far from perfectly, and it definitely improves when there is successful therapy. We have a drug that works, you can see it by improvement in the inflammation.

Now, the stage or the fibrosis changes much more slowly. It is more subject to sampling error in needle biopsies, and there is also no evidence accumulating that that may improve with successful therapy.

[Slide.]

You will also hear during the course of the presentations about ranked assessments of the liver biopsies, and I will tell you how that is done. This is after we have done the semi-quantitative scoring.

I still have the two biopsies together. I

know they are both from the same patient, but I don't know what the patient received, and I don't know which is pre-treatment and post-treatment. I just look at them one after another and say whether there is a difference or not, whether they look about the same or whether one looks better, another one looks worse. We do that both for inflammation and fibrosis. I will show you an example of that.

[Slide.]

Here is for inflammation. Over on the left is biopsy A, on the right is biopsy B. I don't know which is pre-treatment or post-treatment, but you can see there is a lot more inflammation, a lot more interface hepatitis, a lot more parenchymal injury in A than in B, so B is better. That is a ranked assessment.

[Slide.]

Do the same thing for fibrosis. Here is biopsy A, biopsy B. I know they are both from the same patient, but biopsy A has a lot more fibrosis even though some of it is not staining very darkly in this projection, much more fibrosis than biopsy B, so biopsy B looks better.

[Slide.]

So, then the only thing left to do is put

it all together, how can we assess this in a meaningful fashion. Now, the primary endpoint, as you have heard, is the proportion of patients who have had a 2-point improvement in the inflammatory components of the Histology Activity Index with no worsening of their fibrosis score.

That is a little bit different from some previous studies, which did not include the provision for fibrosis, but it doesn't really change the results very much. I just want to comment that that is the absolute most conservative way you can look at the data, because it only looks at the proportion, it doesn't take into account the fact that some patients can get worse and it doesn't take into account the magnitude of the change.

There are other endpoints that can be used, which magnify the difference between the drug and the placebo. There is the ranked assessment. We can look at the mean change in the Index and in the scores.

We can use other scoring systems, but really the bottom line is I have done all of these in different contexts and different studies. The bottom line really is that if the drug works, then,

everything works, that everything will show improvement any way you want to look at the data.

I brought some pictures of actual biopsies from the study, if anyone is really interested in seeing them, I will be happy to show them during the question period.

I will turn it back to Dr. Taylor.

Introduction

Alan Taylor, Ph.D.

DR. TAYLOR: Thank you, Dr. Goodman.

[Slide.]

We will continue with Gilead's formal presentation, which will begin with an introduction to chronic hepatitis B and a summary of key findings from our preclinical, clinical pharmacology, and Phase I/II studies for adefovir dipivoxil.

Dr. Carol Brosgart will then present the efficacy, safety, and virology results of our pivotal studies in e-antigen-positive and e-antigen-negative chronic hepatitis B, and supportive studies in patient with lamivudine-resistant chronic hepatitis B.

[Slide.]

Chronic hepatitis B is an important global

healthcare problem that affects approximately 200 million people worldwide. Two populations with active liver disease are distinguished by serology and natural history. HBe-antigen-positive for chronic hepatitis B is the predominant form, HBe-antigen-negative chronic hepatitis B is seen commonly in Southern Europe and Asia, it is increasing worldwide, and is significant because sustained responses to therapy are rare in this population.

Twenty-five to 33 percent of patients with chronic hepatitis B will have progressive disease over the course of their lifetime, leading to hepatic decompensation, cirrhosis, or hepatocellular carcinoma.

There are 1 million deaths each year resulting from chronic hepatitis B, making it the tenth leading cause of death worldwide. This is also an important problem in the U.S. that affects over 1 million patients, 17,000 hospitalizations and 5,000 deaths result each year from disease complications, and chronic hepatitis B is the sixth leading indication for liver transplantation in adults.

[Slide.]

Treatment options are limited for patients with chronic hepatitis B, with only two therapies approved in the U.S. Interferon-alpha is a cytokine immunomodulator with antiviral activity that requires parenteral administration.

Interferon is poorly tolerated in some patients, has limited activity in e-antigen-negative patients and those with immunosuppression, and is contraindicated in patients with decompensated liver disease.

Lamivudine is an oral nucleoside analog that inhibits HBV replication. Lamivudine is well tolerated, but the emergence of lamivudine-resistant HBV mutants is associated with loss of viral suppression and progression of liver disease, limiting long-term clinical benefit for patients. Patients need additional treatment options.

[Slide.]

New antiviral therapies for chronic hepatitis B need to be safe and well tolerated for long-term use in patients who do not undergo e-antigen seroconversion.

New treatments are needed that are effective in all populations including those who

have compensated and decompensated liver disease, those who are e-antigen- positive, those who are e-antigen-negative, and should be active against all HBV genotypes.

Patients with liver transplantation and drug-resistant virus are especially challenging and need additional treatment options. Importantly, new antiviral therapies should have a high threshold for the development of resistance to provide long-term clinical benefit to patients.

[Slide.]

Adefovir dipivoxil is a new antiviral therapy for chronic hepatitis B that may help address the current unmet medical need.

Adefovir dipivoxil is an oral prodrug of adefovir, a nucleotide analog of adenosine monophosphate with activity against hepadnaviruses, retroviruses, and herpes viruses. The active intracellular metabolite, adefovir diphosphate, is a potent and selective inhibitor of HBV DNA polymerase with an inhibition constant of 0.1 micromolar.

Adefovir diphosphate has a long intracellular half-life, 12 to 36 hours, supporting once daily dosing.

We were unable to identify any adefovir-associated resistance mutations in our preclinical studies. Unlike lamivudine, adefovir-associated resistance mutation sites in the HIV reverse transcriptase, the K65R and K70E are not conserved in HBV DNA polymerase.

Adefovir was active against all the drug-resistant HBV strains that we evaluated in vitro including lamivudine-resistant HBV.

[Slide.]

Mutations in HBV DNA polymerase at the M552I and M552V and the double mutation at L528M and M552V conferred resistance to lamivudine with inhibition constants increasing by 8- to 25-fold compared with wild-type.

In contrast, these mutants remain sensitive to adefovir with KI's increasing by less than 2.3-fold. These data suggested that adefovir dipivoxil might be an effective treatment for patients with lamivudine-resistant chronic hepatitis B.

[Slide.]

Preclinical studies evaluated the in vivo antiviral activity, pharmacokinetics, and toxicology of adefovir dipivoxil. Adefovir

dipivoxil reduced serum viremia in three hepatitis virus animal models - the Duck Hepatitis B Virus Model, the Woodchuck Hepatitis Virus Model, and in transgenic mice expressing HBV.

In the Duck Model, treatment resulted in reduction in viral markers in the liver including cccdNA, a key HBV intermediate responsible for viral persistence. Activity was also demonstrated in the bile duct epithelial cells, an important viral reservoir that was not affected by nucleoside analogs.

The Woodchuck Hepatitis Virus infected woodchuck is an important model for evaluating antiviral activity and the potential for delayed onset hepatotoxicity. Adefovir dipivoxil had no adverse effects on key safety parameters in the woodchuck model.

Pharmacokinetics and target organ toxicity were similar across species. Pharmacokinetics of adefovir are dose proportional following oral administration of adefovir dipivoxil, and adefovir is excreted unchanged in the urine by a combination of glomerular filtration and tubular secretion.

The kidney was the clinically relevant target organ identified in all animal models, and

based on this finding, we have carefully evaluated renal laboratory parameters throughout our HBV program.

[Slide.]

A comprehensive clinical pharmacokinetic program was undertaken that included normal volunteers, patients with chronic hepatitis B and patients with renal and hepatic impairment.

Adefovir dipivoxil has good oral bioavailability and the plasma half-life for adefovir was approximately 7 hours.

Pharmacokinetics were not significantly changed by food, chronic hepatitis B disease, or by patient demographic characteristics including age, gender, ethnicity, or body weight.

Adefovir is not a substrate or inhibitor of the major human cytochrome p450 enzymes in vitro, suggesting low potential for drug interactions based on p450 interaction.

Drug interactions were formerly evaluated for adefovir with four relevant drugs used in chronic hepatitis B patients. No clinically relevant drug interactions were seen for adefovir with lamivudine, acetaminophen, ibuprofen, or trimethoprim sulfamethoxazole.

In a study of pharmacokinetics and renal impairment, increases in adefovir concentration were seen in patients with creatinine clearance less than 50 mL/minute. Patients with moderate to severe renal impairment will require dosing interval adjustment.

No alteration in dosing frequency is necessary for patients with hepatic impairment.

[Slide.]

Four Phase I and II studies were conducted in chronic hepatitis B to assess initial safety and efficacy. Doses of 5 to 125 mg were evaluated. A similar 3 to 4 log reduction in HBV DNA was seen at all doses greater than 5 mg, and was associated with HBe antigen seroconversion and ALT normalization in some patients.

In a prior clinical development program of adefovir dipivoxil evaluating 60 and 120 mg daily, nephrotoxicity was the treatment-limiting adverse event. Nephrotoxicity was well characterized in the HIV program that included over 2,000 patients in controlled clinical trials for up to three years and over 7,000 patients in expanded access.

Based on the nephrotoxicity seen in the HIV program, doses of 60 mg or more were not

considered suitable for chronic administration. Ten and 30 mg were selected for further evaluation in chronic hepatitis B.

With extended dosing in Phase II, we demonstrated sustained antiviral activity and no adefovir-associated resistance mutations were identified.

Therapy with 30 mg for 20 weeks or longer was associated with increased incidence of renal laboratory abnormalities. These were resolved after discontinuation of therapy, and this finding was confirmed in our first Phase III study.

Patients who do not undergo HBe antigen seroconversion will require long-term therapy, 10 mg was selected as our target dose in Phase III because it had potent antiviral activity and a favorable safety profile.

We now have extensive data for adefovir dipivoxil 10 mg in chronic hepatitis B.

[Slide.]

Of the 2,000 patients in our program, over 1,600 patients have received treatment with the 10 mg dose. Of these, 800 patients were studied in our three large studies, in e-antigen-positive and e-antigen-negative chronic hepatitis B, and in

transplantation.

At the time of the NDA safety update, almost 600 patients had received treatment for greater than or equal to 48 weeks, and substantial numbers of patients were treated for longer including over 250 patients treated for at least 96 weeks.

Dr. Carol Brosgart will now present the results of our Phase III studies of adefovir dipivoxil 10 mg, demonstrating safety and efficacy in chronic hepatitis B.

Clinical Efficacy and Safety

Carol Brosgart, M.D.

DR. BROSGART: Good morning.

Adefovir dipivoxil is a significant advance in the treatment of chronic hepatitis B. The global development program for adefovir dipivoxil in the treatment of chronic hepatitis B was conducted in a full range of patient populations in 18 countries throughout North America, Europe, Asia, and Australia.

The data package demonstrates efficacy and safety of the 10 mg dose across all populations studied.

Our two pivotal studies were conducted in

patients with chronic hepatitis B and compensated liver disease.

[Slide.]

Both studies are double-blind, randomized, placebo-controlled trials. Study 437 was conducted in the hepatitis B e-antigen population and enrolled 511 patients who received at least 1 dose of study drug, randomized in a 1 to 1 to 1 ratio to adefovir 30 mg, adefovir 10 mg, and placebo.

Study 438 was conducted in the hepatitis B e-antigen-negative or presumed precore mutant HBV population and enrolled 184 patients who received at least 1 dose of study drug, randomized in a 2 to 1 ratio to adefovir 10 mg or placebo.

The primary endpoint in both studies was improvement in liver histology for adefovir 10 mg as compared to placebo at week 48.

Patients were followed for an additional 48 weeks for safety and efficacy. In the second 48 weeks, patients on adefovir 30 mg received placebo, and those on placebo received adefovir 10 mg. In both studies, the adefovir 10 mg patients were re-randomized after 48 weeks to either continue adefovir 10 mg or to go to placebo in the second 48 weeks.

During the second 48 weeks of the e-antigen- positive study, an error occurred with the drug allocation system. This error was isolated specifically to the e-antigen-positive study in the second 48-week period.

416 e-antigen-positive patients received at least one month of incorrect dosing. Upon discovering this error, we immediately ended the blinded phase of the second 48 weeks of the e-antigen positive study. All the e-antigen positive patients were offered open-label adefovir 10 mg through a protocol amendment.

This presentation will focus first on the adefovir 10 mg data at 48 weeks for the primary and secondary endpoints in the pivotal studies. The 30-mg data will be presented separately.

During the presentation, I will refer to each pivotal study by patient population. Study 437 is the hepatitis B e-antigen positive population, and Study 438 is the hepatitis B e-antigen-negative population.

In addition to sharing similarities of study design and endpoints, the two pivotal share some common key inclusion criteria.

[Slide.]

To be included in study, patients had to have documented evidence of chronic hepatitis B, compensated liver disease, adequate renal function, and no evidence of coinfection with HIV, HCV, or hepatitis delta. Patients had to be willing to undergo a liver biopsy at baseline and at week 48.

The differences in entry criteria for the HBV DNA and ALT reflect the variable nature of viral replication and liver inflammatory activity in these two populations. The treatment assignments within each study were well balanced across individual study arms. These data are included in the Backgrounder. During the presentation I will show the overall baseline characteristics for each study.

[Slide.]

The median age was younger in the e-antigen positive population. Both studies were predominantly male. The e-antigen positive population was two-thirds Asian, the e-antigen-negative population was two-thirds Caucasian. 24 and 41 percent of patients had a prior course of interferon. A small proportion of patients in each study had received a prior short course of lamivudine of less than 12 weeks.

[Slide.]

The baseline hepatitis B disease characteristics are similar across both studies. High levels of viral replication were evident with median serum HBV DNA of 8.4 logs or approximately 250 million copies per mL in the e-antigen positive population, and 7.1 logs or approximately 13 million copies per mL in the e-antigen-negative population.

Alanine aminotransferase levels were 2.3 times the upper limits of normal.

The median Knodell score was 10 in both studies, reflecting mild to moderate necroinflammation and fibrosis. Six and 11 percent of patients had evidence of cirrhosis.

[Slide.]

The primary endpoint in both studies was improvement in liver histology at 48 weeks. The primary endpoint was defined as a reduction of at least 2 points in the Knodell necroinflammatory score with no accompanying worsening in the Knodell fibrosis score.

This analysis was performed with the intent-to-treat population who had an evaluable baseline biopsy. Patients who had missing or

unevaluable post-baseline biopsies were considered treatment failures.

Histology was assessed by one central histopathologist who was blinded both to treatment assignment and to treatment sequence. Eighty-six percent of the e-antigen-positive patients and 91 percent of the e-antigen-negative patients had paired evaluable biopsies at baseline and week 48.

The primary endpoint, histological evaluation of the liver biopsies showed consistent and significant improvements in the adefovir dipivoxil 10 mg groups as compared to placebo.

[Slide.]

In these analyses where adefovir 10 mg patients are displayed in yellow, and placebo patients in gray, a significant treatment benefit is demonstrated for adefovir 10 mg with 53 and 64 percent of the adefovir 10 mg patients having histological improvement compared to 25 and 33 percent of the placebo patients.

Histological improvement was also demonstrated for change from baseline in total and the component Knodell scores for necroinflammation and fibrosis.

Subset analyses of the primary efficacy

endpoint were performed using the integrated database to assess the consistency of treatment effect across baseline, demographic, and hepatitis B disease characteristics.

[Slide.]

These analyses suggest that adefovir confers benefit relative to placebo for histological improvement by all baseline demographic characteristics - gender, ethnicity, and age.

[Slide.]

A benefit for adefovir 10 mg is also seen by baseline hepatitis B disease characteristics. Adefovir 10 mg demonstrated significant improvement compared to placebo regardless of prior interferon use, Knodell score, HBV DNA level, or ALT level.

High baseline ALT and Knodell scores and low HBV DNA were associated with higher absolute rates of histological improvement, however adefovir resulted in significant histological improvement compared to placebo regardless of whether patients had high or low baseline Knodell scores, ALT, or HBV DNA levels.

The treatment benefit was also significant and consistent across all secondary efficacy

endpoints. The secondary endpoints included the ranked assessment of liver histology, change in serum HBV DNA and ALT, and in the e-antigen-positive population, the loss of e-antigen and e-antigen seroconversion.

In both studies, we prospectively evaluated for the emergence of adefovir-related resistance mutations.

In the ranked assessment of histopathology, paired baseline and week 48 biopsies were compared by the histopathologist, who was blinded both to treatment assignment and treatment sequence, and these were graded as being better, worse, or the same.

[Slide.]

The ranked assessment of necroinflammation demonstrated that 71 and 80 percent of adefovir 10 mg patients had improvement in necroinflammation with few patients showing any worsening over the course of 48 weeks. In contrast, far fewer patients in the placebo group demonstrated improvement. Substantial numbers of placebo patients, 34 and 51 percent, were assessed to have worsened necroinflammation over the course of 48 weeks.

[Slide.]

If we look at fibrosis, we see the same pattern. The adefovir 10 mg patients had significantly more improvement in fibrosis. In contrast, a greater proportion of placebo patients, 26 and 38 percent, had worsening of fibrosis over 48 weeks.

[Slide.]

In addition to the ranked assessment, the analyses of change from baseline in Knodell and Ishak fibrosis scores revealed that adefovir 10 mg patients had more regression and less progression of fibrosis than the placebo patients. This is very important clinically, because the development of fibrosis is the hallmark of progression of liver disease.

[Slide.]

An important goal of therapy for chronic hepatitis B is the suppression of viral replication and the prevention of progression of liver disease. In both studies, patients treated with adefovir 10 mg have a rapid, approximate 2 log decline in serum HBV DNA by week 4 that continues to decline progressively throughout study.

At 48 weeks, adefovir 10 mg patients have a 3.5 and 4 log reduction in serum HBV DNA,

compared to a 0.55 and 1.35 log reduction in the placebo group. This treatment difference favoring adefovir was highly significant.

We evaluated changes in serum HBV DNA by PCR using the Roche Amplicor assay with a lower limit of quantification of 400 copies/mL. This is notably different from assays used in different clinical drug development programs for the treatment of chronic hepatitis B, which used assays with a higher lower limit of quantification ranging from 700,000 to over 1 million copies/mL.

[Slide.]

We evaluated the proportion of patients with undetectable levels of serum HBV DNA below 400 copies/mL following 48 weeks of adefovir 10 mg therapy. At week 48, 21 and 51 percent of adefovir 10 mg patients had undetectable serum HBV DNA.

No placebo patient treated in either the e-antigen-positive or the e-antigen-negative study achieved an undetectable serum HBV DNA. The difference between studies is likely to be a reflection of the lower baseline levels of HBV DNA seen in the e-antigen-negative population.

[Slide.]

Elevations of serum alanine

aminotransferases correlate with active liver inflammation. ALT normalization is an important clinical measure of treatment outcome. Forty-eight and 72 percent of the adefovir 10 mg patients had normalized ALT levels at 48 weeks.

A pattern of rapid and progressive decline in ALT is observed, similar to the pattern seen with serum HBV DNA reduction.

[Slide.]

Hepatitis B e-antigen loss and seroconversion are clinical markers of an improved immunological response to chronic hepatitis B disease. Significantly more adefovir-treated patients had either lost e-antigen or had undergone e-antigen seroconversion at 48 weeks.

The majority of patients with chronic hepatitis B will require long-term therapy.

[Slide.]

We designed our pivotal studies to look at the safety and efficacy of continued adefovir 10 mg therapy beyond 48 weeks. Additional improvement is observed for all specified efficacy parameters with continued adefovir 10 mg therapy.

[Slide.]

Patients who continued adefovir 10 mg in

the second 48 weeks of both studies had not only sustained but further reductions in serum HBV DNA. By week 72, Kaplan-Meier estimates for serum HBV undetectability were 46 and 80 percent, and 78 and 81 percent of patients had normalized ALT. In the e-antigen-positive population, 44 percent achieved e-antigen loss and 23 percent undergo fully antigen seroconversion.

The data in the two pivotal studies are robust in that the results are consistent for the primary and all secondary efficacy endpoints.

[Slide.]

Treatment with adefovir 10 mg once daily resulted in highly significant improvement in liver histology, the primary endpoint, and in all secondary efficacy endpoints including serum HBV DNA reduction, the proportion of patients with undetectable serum HBV DNA, ALT normalization, and with e-antigen loss and e-antigen seroconversion in the e-antigen-positive populations.

Histological improvements were similar when analyzed by all baseline and hepatitis B disease characteristics. There is continued improvement in all efficacy parameters with dosing beyond 48 weeks.

[Slide.]

Adefovir 10 mg demonstrated a safety profile generally similar to placebo in the pivotal studies. We will examine the safety in the pivotal studies both by individual study and through integrated analyses of safety.

[Slide.]

For each study, the overall safety experience for the incidence of adverse events and discontinuation rates was similar between adefovir 10 mg and placebo. Safety was similar when examined by all baseline, demographic, and hepatitis B disease characteristics.

The database for the e-antigen-positive and the e-antigen-negative populations was integrated to increase the ability to detect safety signals.

[Slide.]

The incidence of Grade 1 through 4 treatment-related adverse events that occurred in at least 3 percent or more of adefovir 10 mg patients was similar to those observed in patients treated with placebo.

[Slide.]

There is a similar pattern demonstrated

for Grade 3 and 4 laboratory abnormalities. Six Grade 3 or 4 laboratory abnormalities occurred in at least 1 percent or more of patients treated with adefovir 10 mg. The incidence of Grade 3 or 4 laboratory abnormalities including hematuria and glycosuria observed in patients treated with adefovir 10 mg appears similar to that of placebo.

Severe elevations of ALT and AST occurred more frequently in placebo-treated patients.

[Slide.]

As nephrotoxicity was the most important treatment-limiting adverse event identified with higher doses of adefovir in the HIV development program, we carefully monitored renal laboratory abnormalities throughout the HBV program.

For these 7 renal laboratory parameters, the incidence of Grades 1 through 4 abnormalities is similar to adefovir 10 mg and for placebo. Aside from hematuria and glycosuria, all abnormalities in either the adefovir 10 mg patients or the placebo patients were at Grade 2 or below.

[Slide.]

Based on our experience at higher doses, changes in serum creatinine and serum phosphorus are the most sensitive and specific laboratory

markers of adefovir-related nephrotoxicity.

The protocol required patients to be permanently discontinued from study drug for any increase of serum creatinine greater or equal to 0.5 mg/dL above baseline or any decrease in serum phosphorus to less than 1.5 mg/dL as confirmed by two consecutive laboratory assessments.

Over 48 weeks, no adefovir 10 mg or placebo patient had either of these events. Additionally, the median change in serum creatinine values was zero, and there was a 0.1 mg/dL median increase in serum phosphorus in both groups.

[Slide.]

We have subsequently examined the database looking at more conservative thresholds for serum creatinine and serum phosphorus. In the e-antigen-positive population, a confirmed increase in serum creatinine greater or equal to 0.3 mg/dL above baseline was seen in 5 percent of adefovir 10 mg patients and 1 percent of placebo.

However, the opposite is observed in the e-antigen-negative study with 5 percent of placebo patients as compared to 2 percent of adefovir 10 mg patients having this renal laboratory abnormality. Confirmed changes in serum phosphorus less than 2

mg/dL were only seen in the placebo e-antigen-positive group.

[Slide.]

With maximum adefovir 10 mg exposures in these pivotal studies up to 109 weeks, the safety profile observed with continued adefovir 10 mg dosing beyond 48 weeks is consistent with the experience in the first 48 weeks.

After 48 weeks, there is no longer a placebo comparator, so it is difficult to put into perspective any further changes. Over the 96-week study, 6 percent or a total of 29 of the 492 adefovir 10 mg patients have a confirmed increase in serum creatinine greater or equal to 0.3 mg/dL above baseline.

This is consistent with the incidence observed in either the placebo or the adefovir 10 mg arms during the first 48 weeks. Beyond 48 weeks, less than 1 percent of patients treated with adefovir 10 mg are reported to have a confirmed increase in serum creatinine greater or equal to 0.5 mg/dL above baseline.

There were no adefovir 10 mg patients with a confirmed change in serum phosphorus at less than 1.5 or less than 2.0 mg/dL.

[Slide.]

We examined the 29 adefovir 10 mg patients who have confirmed increases in serum creatinine greater or equal to 0.3 mg/dL above baseline through 96 weeks. Of the 2 patients, 20 resolved while continuing on adefovir 10 mg dosing. Serum creatinine in 8 patients was stable with continued adefovir 10 mg dosing. Only 2 of the 29 patients had increases greater than or equal to 0.5 mg/dL above baseline. Both of these patients resolved, 1 with continued dosing of adefovir 10 mg, and 1 within 4 weeks of discontinuing adefovir.

These changes in serum creatinine were not accompanied by other changes in renal laboratory parameters. Changes in serum creatinine greater or equal to 0.5 mg/dL appears to be an appropriate threshold for the evaluation of potential nephrotoxicity in patients with normal renal function.

The incidence of renal laboratory abnormalities were similar for adefovir 10 mg and placebo through 48 weeks. The incidence of renal laboratory abnormalities through week 96 is similar to that observed in the first 48 weeks.

[Slide.]

Elevations in ALT during treatment may indicate ongoing hepatitis B disease activity and immunological response to therapy or potentially drug toxicity. Over the course of 48 weeks, Grade 4 or severe ALT elevations occurred more frequently in the placebo group.

The protocol defines severe hepatic flares as elevations in ALT greater than 10 times the upper limits of normal, accompanied by at least one other parameter of liver function including an increased serum bilirubin, a decreased serum albumin, or a prothrombin time that was prolonged above the upper limits of normal.

During the first 48 weeks, no patient treated with adefovir 10 mg had a severe hepatic flare. In contrast, patients treated with placebo had Grade 4 ALT elevations that were accompanied by severe hepatic flares indicative of chronic hepatitis B disease activity in the absence of antiviral suppression.

[Slide.]

In the lamivudine hepatitis B development program, discontinuation of lamivudine was associated with severe hepatic flares in some patients. We prospectively evaluated the safety of

adefovir 10 mg following discontinuation of treatment.

The incidence of Grade 4 ALT elevations remained unchanged in patients who continued adefovir 10 mg beyond 48 weeks. Twenty-five percent of patients who were initially randomized to adefovir 10 mg in the first 48 weeks and then switched by protocol to placebo in the second 48 weeks experienced Grade 4 ALT elevations.

The experience upon discontinuing therapy appears similar to that of the placebo-treated patients during the first 48 weeks of study, consistent with ongoing active liver disease of untreated chronic hepatitis B.

The onset of ALT elevations was generally within 4 to 12 weeks after switching from adefovir 10 mg to placebo. In all cases, ALT elevations were associated with increases in serum HBV DNA accompanied by e-antigen loss in 1 patient and by an increase in serum bilirubin in 3 percent of the patients.

These ALT elevations were generally self-limited or resolved upon reinitiation of antiviral therapy. None of these patients developed decompensated liver disease.

[Slide.]

Overall, the safety and tolerability of adefovir 10 mg was similar to placebo through 48 weeks. Severe increases in ALT and AST, reflective of ongoing active hepatitis B disease activity, were seen more frequently in the placebo group in the first 48 weeks.

The safety profile of adefovir 10 mg beyond 48 weeks was consistent with that observed through 48 weeks. Through 96 weeks, the incidence of serum creatinine increase was very low, with 1 patient out of 492 treated with adefovir 10 mg discontinuing therapy for a serum creatinine increase.

There was no evidence of hypophosphatemia.

If adefovir treatment is discontinued, patients should be monitored carefully for at least 12 weeks for signs of exacerbation of hepatitis B post-treatment.

[Slide.]

The e-antigen-positive study included an adefovir 30 mg arm in the first 48 weeks. Although this study was not prospectively designed to compare adefovir 30 mg directly with 10 mg, one of the important things we were able to learn was the

relative difference in the risk-benefit profile of adefovir 30 mg compared to adefovir 10 mg.

[Slide.]

There is consistent benefit for adefovir both 10 and 30 mg as compared to placebo for the primary endpoint of histological improvement and for all secondary endpoints - change in HBV DNA and HBV DNA undetectability, change in ALT and ALT normalization, and e-antigen loss and e-antigen seroconversion.

The Backgrounder has detailed data by treatment arm. There appears to be a slightly better response in the adefovir 30 mg group for all efficacy parameters evaluated, however, there are important differences in the safety profiles of adefovir 10 and adefovir 30 mg.

A higher incidence of adverse events, treatment-related adverse events, and discontinuations were observed with adefovir 30 mg than with adefovir 10 mg. Importantly, renal laboratory abnormalities were observed with the adefovir 30 mg dose during 48 weeks of treatment.

[Slide.]

Seven percent of the adefovir 30 mg arm had confirmed increases in serum creatinine greater

or equal to 0.5 mg/dL above baseline compared to none in the adefovir 10 mg arm. While no 30 mg patient had confirmed decreases in serum phosphorus less than the 1.5 mg/dL level, 5 percent had confirmed decreases in serum phosphorus less than 2 mg/dL.

The time of onset for the increase in serum creatinine at the 30 mg dose was similar to that seen with higher doses of adefovir in the HIV program, however, the observed incidence and severity of these increases was much lower on adefovir 30 mg.

[Slide.]

While both doses showed significant efficacy, the 30 mg dose was associated with an increased incidence of adverse events and renal laboratory abnormalities. Adefovir 10 mg has a more favorable risk-benefit profile for long-term dosing in chronic hepatitis B patients.

[Slide.]

The emergence of drug resistance to therapies for chronic hepatitis B limits the durability of treatment response. Resistance to lamivudine in the treatment of hepatitis B first occurs following at least 24 to 36 weeks of

therapy.

Throughout the adefovir clinical development program for hepatitis B, we have prospectively monitored for the emergence of adefovir-related resistance mutations. We have not identified adefovir-associated resistance mutations in patients in the pivotal studies through 48 weeks of therapy.

[Slide.]

In the pivot studies, we conducted a prospective, comprehensive, blinded resistance surveillance program that included genotypic, phenotypic, and clinical evaluations. We sequenced the entire reverse transcriptase domain of the HBV DNA polymerase at baseline and week 48, and compared them to identify potential treatment emergent substitutions.

For substitutions identified in conserved regions, we created site-directed mutants that could be evaluated phenotypically for in vitro susceptibility to adefovir.

If the HBV DNA in patient samples at week 48 was undetectable, less than 400 copies/mL, sequencing was not possible. Paired baseline samples were therefore available for the evaluation

of resistance in 498 of the 695 patients in the pivotal studies.

[Slide.]

Prior to unblinding, conserved site substitutions were identified in 10 patients. None of the substitutions were associated with phenotypic resistance in vitro. Once we had unblinded the study, we found that 6 of the 10 patients had received placebo, 3 in the e-antigen-positive study and 3 in the e-antigen-negative study.

Of the 4 adefovir patients that had substitutions, all were in the e-antigen-positive study. Two were treated with adefovir 30 mg and two with adefovir 10 mg. Each patient had only 1 substitution and no substitutions occurred in more than 1 patient.

The 4 adefovir-treated patients with substitutions had an approximate 4 log reduction in serum HBV DNA consistent with the response seen in the overall adefovir-treated patient, and had no evidence of viral rebound.

In summary, there were no adefovir-associated resistance mutations identified up to 48 weeks. Our preclinical data suggested

that adefovir had similar activity against wild-type and lamivudine-resistant HBV.

[Slide.]

Results from 5 supportive studies are reported in the NDA in which adefovir 10 mg once daily is administered to populations of patients with chronic hepatitis B and evidence of diminished therapeutic response to lamivudine.

[Slide.]

The incidence of lamivudine resistance reported from a meta-analysis of the 3 lamivudine registrational studies is approximately 24 percent after 1 year of treatment and increases to 69 percent with patients treated up to 5 years.

Lamivudine resistance has been associated with a diminished therapeutic benefit including loss of HBV DNA suppression, elevations in ALT, and loss of histological benefit. These ALT elevations may be severe and in some patients have resulted in liver decompensation, loss of liver graft, and death.

There are no licensed therapies for the treatment of lamivudine-resistant HBV. We initially provided compassionate access to adefovir to treat patients with lamivudine-resistant HBV on

a case-by-case basis.

[Slide.]

In 1999, in response to the growing demand, we initiated an open-label, compassionate access study. Study 435 was conducted in patients post-liver transplantation and then later the protocol was amended to include patients wait-listed for liver transplantation.

To date, 463 patients have been enrolled worldwide, 324 of these patients were included in the NDA safety update. Our hepatology consultants here with us today have cared for some of these medically compromised patients and are available to provide a clinical perspective during the question and answer period.

[Slide.]

Prior to the availability of specific therapies, one year survival rates were low in patients with decompensated cirrhosis due to chronic hepatitis B and in patients post-transplantation due to reactivation of hepatitis B.

Therapy with interferon-alpha is contraindicated in these populations. Survival improved with the availability of lamivudine in

both populations and with hepatitis B immune globulin for prevention of reinfection post-transplantation.

This therapeutic benefit is unfortunately not sustained in all patients and diminishes with the emergence of resistance. An open-label compassionate access study was conducted because of the urgent medical need in this patient population who were failing lamivudine therapy.

It would have been unethical to randomize these patients to placebo given their imminent risk of disease progression and there are no commercially available comparators for the treatment of lamivudine-resistant HBV.

Patients with clinical evidence of lamivudine failure received open-label adefovir 10 mg daily. Ongoing lamivudine was permitted at the investigator's discretion.

[Slide.]

These are the baseline characteristics of the two cohorts in the transplantation study. We have baseline data for 196 post-transplantation patients and 128 pre-transplantation patients.

The population is older than that seen in the pivotal studies and patients in both groups

have lost therapeutic response to lamivudine approximately 1 to 1 1/2 years prior to study entry.

Renal function was compromised with many patients having elevated serum creatinine levels at baseline.

These post-transplantation patients were approximately 4 years out from their liver transplantation with long exposures to cyclosporine and/or tacrolimus. These two immunosuppressive agents are associated with both acute and chronic nephrotoxicity. Comorbidities were present in the majority of patients.

The study began prior to the availability of the adefovir dosing guidelines that have emerged from our pharmacokinetic study conducted in patients with varying degrees of renal impairment.

As a result, some of the transplantation patients with baseline renal impairment may have had increased adefovir exposure.

[Slide.]

There are similarities and important differences in the hepatitis B disease characteristics between the liver transplantation patients and patients with compensated liver

disease in the pivotal studies.

Transplantation patients had high levels of HBV viral replication at study entry, 8.2 and 7.4 logs, similar to that seen in the pivotal studies. The median ALT was two times the upper limit of normal.

In patients with decompensated liver disease, an overall assessment of clinical status is determined with the Child-Pugh-Turcotte score or the CPT score. A significant proportion of patients in each cohort had decompensated liver disease at baseline as evidenced by CPT scores greater than or equal to 7, elevated serum bilirubin, decreased serum albumin levels, and prolonged prothrombin time.

[Slide.]

Substantial efficacy was demonstrated in these 324 pre- and post-liver transplantation patients with lamivudine-resistant HBV treated with adefovir 10 mg. As seen in the pivotal studies, with the addition of adefovir 10 mg, there is an immediate response, an approximate 2 log decline by week 4, that continues throughout study with a greater than 4-log reduction in serum HBV DNA demonstrated at 48 weeks.

[Slide.]

Significant improvement was demonstrated in all efficacy parameters. At week 48, serum HBV DNA had become undetectable in 34 and 81 percent of patients. In patients with abnormal liver function at baseline, ALT, serum albumin, and serum bilirubin had normalized in the majority of patients. Prothrombin time had normalized in 20 and 83 percent of patients. The CPT score was stable or improved in 96 and 92 percent of patients.

[Slide.]

While there was consistent improvement in all of these efficacy parameters, what is of the utmost importance to patients and physicians is survival. One-year survival is estimated in 93 percent of post-transplantation patients and in 84 percent of patients who are wait-listed for transplantation.

Although many of these patients were compromised secondary to advanced liver disease and comorbidities, few patients discontinued study. Discontinuation rates were similar in each cohort.

[Slide.]

The post-transplantation patients were

followed for a median of 56 weeks up to a maximum of 129 weeks. The pre-transplantation patients had a shorter duration of follow-up, 19 weeks up to a maximum of 72 weeks.

Reasons for early termination included adverse events in 2 percent of patients and death in 7 and 5 percent of the patients. Generally, the deaths occurred early in the first 24 weeks of study and were considered by the investigators to be due to complications of progressive liver disease or to liver transplantation surgery, and unrelated to adefovir.

In two cases, while the investigator assessed the deaths as being due to the progression of underlying liver disease, the investigators could not rule out a potential contributory role of adefovir.

[Slide.]

Renal laboratory abnormalities were observed in 41 transplantation patients. Twenty-six post-transplantation and 15 pre-transplantation patients were identified with confirmed increases in serum creatinine greater or equal to 0.5 mg/dL above baseline through 96 weeks.

Hypophosphatemia less than 1.5 mg/dL was

observed in 1 patient which resolved with continued dosing.

We have evaluated individually the 26 post- and the 15 pre-transplantation patients with changes in serum creatinine to determine the potential contributory role of adefovir. Additionally, we have had two nephrologists, independent and external to Gilead, each independently review these cases, Dr. Paul Klotman of Mt. Sinai Medical Center and Dr. Bruce Molitoris of Indiana University.

[Slide.]

The 26 post-transplantation patients had one or more risk factors at baseline for increases in serum creatinine. All were on concomitant cyclosporine and/or tacrolimus. Medical history of renal disease, hypertension, diabetes, or decompensated cirrhosis were present in over half of the cases.

A third of the patients had moderate to severe renal impairment and were not dosed according to the current dose interval guidelines.

In 80 percent of the patients, after the initiation of adefovir 10 mg therapy, and just prior to the observed increase in serum creatinine,

there was further decompensation in cirrhosis or the addition of aminoglycosides or other nephrotoxic agents, or important acute serious medical events including, but not limited to, acute graft rejection, retransplantation of a second liver graft, other major surgeries, sepsis, acute gastrointestinal bleeds, and severe dehydration.

[Slide.]

In the 15 pre-transplantation patients, there were also significant serious medical events prior to the observed increases in serum creatinine. In 11 patients, liver transplantation surgery, the initiation of concomitant cyclosporine and/or tacrolimus, and in some cases, the addition of other nephrotoxic agents, such as aminoglycosides or amphotericin, occurred just prior to the changes in serum creatinine.

In 3 patients, changes in serum creatinine followed further decompensation in liver disease, and in the last patient, the event occurred during follow-up, but 3 months following the last dose of adefovir and was not considered to be treatment emergent.

[Slide.]

The extent to which adefovir contributed

to each serum creatinine increase is difficult to assess in the face of numerous other risk factors present at baseline or just prior to the increase.

It is clear that some patients with creatinine clearance less than 50 mL/minute had increased adefovir exposures comparable to the higher dose exposures associated with nephrotoxicity.

Given the impact of renal impairment on adefovir clearance, we have included in the proposed package insert the recent dosing interval guidelines that have emerged from our pharmacokinetic study in renal impairment and specific precautionary statements regarding adefovir use with concomitant nephrotoxic agents.

In patients with renal impairment or with a risk for renal impairment, creatinine clearance must be evaluated at baseline prior to initiating therapy to establish the initial adefovir dosing interval.

Renal function must be carefully monitored while on therapy with a monitoring frequency tailored to the patient's individual medical status.

For changes in creatinine clearance during

treatment, the dose intervals should be adjusted as appropriate.

Substantial benefit was observed in patients both pre- and post-liver transplantation with lamivudine-resistant HBV for whom there are no current therapeutic options.

[Slide.]

The efficacy observed in the patients pre- and post-transplantation was comparable to that seen in the pivotal studies for change in HBV DNA and ALT. Additional benefit was demonstrated in this population with more advanced liver disease through improvement in overall liver function including normalization of albumin, bilirubin, and prothrombin time. This was reflected in improvements in the Child-Pugh-Turcotte scores.

In the post-transplantation patients, paired baseline and week 48 samples were genotyped, and no adefovir-associated resistance mutations were identified through 48 weeks. This is discussed in detail in the Backgrounder.

The safety profile was consistent with the advanced stage of liver disease and with the attendant comorbidities.

In this patient population with or at risk

for renal dysfunction, renal function must be carefully assessed both prior to and during therapy, and appropriate dose interval adjustments based on dosing guidelines should be followed.

The survival experience in the patients pre- and post-transplantation, together with the improvement in HBV DNA and the other efficacy parameters, is evidence of a clinically meaningful benefit.

Overall, there is a favorable risk-benefit profile for patients wait-listed for transplantation or post-transplantation with lamivudine-resistant HBV.

[Slide.]

Additional supportive studies were conducted in other populations of patients with lamivudine-resistant HBV. These included two open-label studies in high-risk patient populations where adefovir was added to ongoing lamivudine therapy, one in patients with HIV coinfection and one in patients with decompensated cirrhosis.

We have also conducted two active control studies, Study 465 and Study 461, in patients with compensated liver disease and lamivudine-resistant HBV where there is less risk of imminent disease

progression.

The safety and efficacy profile observed in these open-label and controlled studies in patients with lamivudine-resistant HBV is consistent with that of patients seen in the pivotal studies.

No adefovir-associated resistance mutations have been observed in the HIV reverse transcriptase or in the HBV DNA polymerase of the patients with HIV coinfection treated up to 96 weeks.

All of these studies enrolled patients with normal renal function. No renal laboratory abnormalities were observed in these four lamivudine-resistant HBV studies. This includes 48 weeks of follow-up in the patients with decompensated cirrhosis and up to 96 weeks in patients with HIV coinfection, and 48 weeks in each of the patients with compensated liver disease.

The safety profile and the efficacy profiles for these studies are discussed in detail in the Backgrounder. I will only present some key efficacy data from Study 461.

[Slide.]

This study in patients with compensated

liver disease allowed us to assess the independent contribution of adefovir in the treatment of patients with lamivudine-resistant HBV.

Patients were randomized in a double-blind fashion in a 1:1:1 ratio to either continue on lamivudine, to have adefovir added to ongoing lamivudine, or to discontinue lamivudine and to switch to adefovir monotherapy.

Baseline median HBV DNA was 8.1 logs and ALT was 2 times the upper limit of normal. The primary endpoint, change in HBV DNA at week 16, was reported in the NDA. The 48-week results have recently become available, but have not yet been reviewed by the agency.

For patients continued on lamivudine, noted in white, there was no change in serum HBV DNA over 48 weeks. A rapid decline of 2 logs was observed in either of the adefovir-treated arms at 4 weeks, and this continues to decline over the course of study in either adefovir arm.

At week 48, similar to what was seen in the pivotal studies, there was a 3.6 log reduction in the adefovir added to ongoing lamivudine arm, demonstrated in green, and a 4 log reduction in the adefovir monotherapy arm in yellow.

[Slide.]

The reductions in ALT were also consistent with those observed in the pivotal studies. Similar rates of ALT normalization were observed. Fifty-three and 47 percent of both the adefovir-treatment arms underwent ALT normalization at 48 weeks.

When lamivudine was continued as monotherapy, only 5 percent of patients normalized to ALT.

[Slide.]

Long-term safety and efficacy including monitoring for the potential emergence of resistance is the major focus of our further studies.

Adefovir 10 mg e-antigen-positive and e-antigen- negative patients in our pivotal studies will be followed for long-term safety and efficacy for up to 5 years.

Patients who seroconverted in the e-antigen- positive study have been enrolled in an observational off-treatment study to evaluate the durability of seroconversion.

Chronic hepatitis B patients with varying degrees of renal impairment or on dialysis are

being enrolled in a long-term safety and efficacy study where patients will now be dosed according to the new adefovir dosing interval guideline.

We are further evaluating the safety and efficacy of adefovir dipivoxil in special populations. We are beginning our pediatric development program. We deferred the development of adefovir in pediatrics until we had demonstrated the safety and efficacy of adefovir 10 mg, our target registration dose in adults.

The pediatric Phase I dose escalation study will be opened this fall to be followed shortly thereafter by the Phase II safety and efficacy study.

New studies will evaluate other patient populations that were underrepresented in the pivotal studies. As pregnant women were excluded from the pivotal studies, we have initiated a new pregnancy registry for hepatitis B through the antiretroviral pregnancy registry to evaluate the safety of adefovir in pregnant women and in fetal outcomes.

We are working to increase the numbers of African-American and Hispanic patients enrolled in ongoing and future studies.

We will be conducting a number of other drug interaction studies including an evaluation of cyclosporine and tacrolimus.

We are conducting additional controlled studies in HIV coinfection in collaboration with the AIDS clinical trial group.

Studies are ongoing or planned in combination therapy in treatment-naive chronic hepatitis B patients. These evaluate either the combination of adefovir and lamivudine, adefovir and emtricitabine, or adefovir and pegylated interferon.

We will continue our prospective resistant surveillance program to monitor for the emergence of resistance to adefovir in all of our studies. These evaluations include genotypic, phenotypic, and clinical evaluations.

[Slide.]

The results obtained from our global development program provide substantial evidence of the efficacy and safety of adefovir 10 mg in a broad range of patient populations with chronic hepatitis B.

Efficacy and safety were demonstrated in e-antigen-positive and e-antigen-negative patients

with chronic hepatitis B and compensated liver disease, both treatment-naive and treatment-experienced, and in all populations studied with lamivudine-resistant HBV.

The overall efficacy response is consistent across all parameters and all studies and in every patient group evaluated including populations in whom current treatments are considered contraindicated or inadequate.

To date, no adefovir-associated resistance mutations have been identified in patients treated up to 48 weeks in both the pivotal studies and the lamivudine-resistant transplantation study, up to 96 weeks in the HIV coinfection study, and up to 136 weeks in the small Phase II extension study.

The consistency of the resistance profile across all studies, including those in immunocompromised patients, is reinforced by the durability of the treatment response and the continued improvement seen beyond 48 weeks of therapy.

There is a strong need for new therapeutic options with demonstrated efficacy, safety, and a high threshold for the development of resistance in the treatment of the broad range of populations

with chronic hepatitis B.

The consistent response to adefovir 10 mg and the favorable risk-benefit profile support the following proposed indication.

[Slide.]

Adefovir dipivoxil is indicated for the treatment of chronic hepatitis B in adult patients with evidence of active liver disease.

Thank you.

DR. GULICK: Thanks, Dr. Brosgart, and also thanks to Drs. Taylor and Goodman. We are going to hold questions for the sponsor until after the agency's presentation after the break.

We will now break, reconvening at 10:15.

[Break.]

DR. GULICK: The agency will make their presentation. Dr. Bhore and Dr. Nguyen.

FDA Presentation

Rafia Bhore, Ph.D.

DR. BHORE: Good morning. My name is Rafia Bhore. I am a statistician.

[Slide.]

I would like to begin the FDA presentation this morning with some comments on patient demographics of Studies 437, 438, and 435. Next, I

will present our assessment on the efficacy data of Studies 437 and 438.

Dr. Tan Nguyen will then present a discussion on the treatment effect on fibrosis. This will be followed by a review of safety data and some observations on viral resistance.

We will conclude our presentation with a risk-benefit assessment of adefovir for the treatment of chronic hepatitis B. Finally, we will present to the committee a number of pertinent questions for discussion and recommendations.

[Slide.]

Based on serologic data of chronic hepatitis B from the National Health and Nutritional Examination Survey 3, McQuillan, et al., at the National Center for Health Statistics, the prevalence of hepatitis B virus infection in the U.S. was significantly higher among African-Americans and Hispanics than in Caucasians.

The 28 U.S. sites in Study 437 enrolled 15 African-Americans or 10 percent of patients, and those in Study 435 enrolled only 2 African-Americans. A total of 5 patients in these two studies were classified as "Other."

It is unclear as to what this meant. It

appears, therefore, that the African-Americans, Hispanic-Americans, American Indians, and Alaska Natives were significantly underrepresented in the applicant's drug development program.

[Slide.]

Now, I would like to present our assessments on the efficacy data of the two pivotal studies 437 and 438.

[Slide.]

I would like to echo the applicant's findings that the primary efficacy endpoint, that is, histologic improvement at week 48, was met in both Studies 437 and 438. As was mentioned earlier, histologic improvement was defined as a 2-point or more decrease in Knodell necroinflammatory score without worsening of fibrosis.

Both adefovir 10 mg and 30 mg doses showed a statistically significant improvement in histology relative to placebo. A positive treatment effect with respect to fibrosis was also observed. This will be discussed in more detail later by Dr. Tan Nguyen.

[Slide.]

With respect to the Knodell necroinflammatory score, adefovir treatment

resulted in a statistically significant treatment effect compared with placebo, as shown in this slide for Study 437.

The two sets of box plots show data for the entire patient population in Study 437. The left set shows box plots for each treatment group, placebo, 10 mg and 30 mg at baseline, and the right set shows week 48 scores for each treatment group, placebo, 10 mg and 30 mg.

The shaded areas in each box plot show the median scores and a 95 percent confidence interval around the median.

As seen here, the adefovir 10 mg dose shows a statistically significant reduction in median necroinflammatory score from baseline to week 48.

[Slide.]

The same is true with the adefovir 30 mg group that is a statistically significant reduction in median score was observed from baseline compared to week 48.

[Slide.]

Similar findings were also apparent in Study 438, as shown here. A statistically significant reduction in the median

necroinflammatory score was observed in the adefovir 10 mg group from baseline to week 48, when the entire patient population data was analyzed.

[Slide.]

With respect to the Knodell fibrosis score, when the data for the entire patient population were analyzed for Study 437, there was no significant change from baseline in the median scores for any treatment group, however, there are fewer patients in the adefovir 10 mg and 30 mg groups that had a score greater than 1 point at week 48 compared with placebo. This implies that fewer patients had worsening of fibrosis relative to placebo.

Alternatively, this type of data can be assessed by comparing the change from baseline in fibrosis scores for individual patients. This type of analysis regarding fibrosis scores will be discussed by Dr. Nguyen in the presentation that will follow.

[Slide.]

Similar conclusion is made regarding Study 438 with respect to Knodell fibrosis scores when the entire patient population data was analyzed. Although the median Knodell fibrosis scores did not

change from baseline to week 48, the adefovir-treated group had a greater proportion of patients who showed improvement in fibrosis as will be shown later.

[Slide.]

The secondary efficacy endpoint of serum HBV DNA was also met in both Studies 437 and 438. Adefovir treatment resulted in a statistically significant suppression of serum HBV DNA compared with placebo.

In Study 437, at week 48, treatment with adefovir 30 mg resulted in a mean reduction of 4.38 log in HBV DNA from baseline, and 3.52 log mean reduction with the 10 mg group.

In Study 438, the mean change from baseline in HBV DNA in the 10 mg group was 3.54 log at week 48, while that for the placebo group was 1.23 log reduction.

We would like to point out that the viral suppression in patients who received adefovir 10 mg daily dose was approximately 0.9 log less than those who received adefovir 30 mg daily dose at week 48.

Furthermore, an additional 0.5 log in HBV DNA was observed on an average when patients were

treated with adefovir 10 mg beyond 48 weeks. This was based on the as-treated population in Year 2.

When adefovir treatment was discontinued, the HBV DNA levels returned to levels close to baseline.

[Slide.]

This is a graph of serum HBV DNA levels over time for Study 437. This part of the graph shows data for the first 48 weeks and this part shows data for the second 48 weeks. The circles represent the group who switched from placebo to 10 mg.

The filled red squares represent the group who continued on the 10 mg daily dose. The empty orange squares are the group who switched from 10 mg to placebo, and the filled blue triangles are the group that switched from 30 mg to placebo.

During the first 48 weeks, the HBV DNA levels for the adefovir 30 mg group were statistically significantly lower than that for the adefovir 10 mg group.

Due to study medication dosing errors that occurred in Study 437 during the second 48 weeks, the data in this part are difficult to interpret. Patients were therefore switched later to open

label 10 mg dose.

In this slide, a salient point is that when patients were switched from adefovir treatment, either 10 mg or 30 mg, to placebo, the serum HBV DNA levels returned to levels closer to baseline within 4 to 8 weeks.

[Slide.]

In this slide of serum HBV DNA through 76 weeks of data in Study 438, viral replication was suppressed during treatment. However, the treatment effect quickly disappears upon discontinuation of the study drug within 4 to 8 weeks.

[Slide.]

With regard to serum ALT levels, adefovir treatment resulted in a greater progressive decrease in serum ALT over time relative to placebo.

The proportion of patients with normalization of ALT at week 48 was higher in the adefovir groups than those in the placebo group.

Upon discontinuation of the study drug, serum ALT levels peaked within 2 to 3 months.

[Slide.]

Here is a plot of serum ALT over time for

Study 437. There was little separation between the curves for the adefovir 30 mg group, which is in the blue triangles, and adefovir 10 mg group, which is in the red and orange squares.

Patients in the placebo group also experienced some improvement in ALT during the first 48 weeks. Again, due to study medication dosing errors that occurred in Study 437, the data in the second 48 weeks are difficult to interpret.

[Slide.]

Serum ALT levels peaked within 2 to 3 months when patients on adefovir treatment were switched to placebo. The improvement in serum ALT was more pronounced in Study 438 in the placebo group.

We do not have a good explanation of this phenomenon. It could potentially be due to the naturally fluctuating disease course observed in HBe-antigen-negative patients. Perhaps it could be that these patients were more symptomatic as indicated by the high serum ALT at baseline and hence, they were easily identifiable for enrollment.

Now, I would like to yield to Dr. Tan Nguyen, who will continue with our presentation.

DR. NGUYEN: Thank you, Rafia. Finally, you got my name right.

The Advisory Committee members and guests, I would like to turn your attention to the results of our sub-analysis on the treatment effect of adefovir on fibrosis.

[Slide.]

As you will recall, the population-based analysis shown by Dr. Bhore did not reveal substantial changes in the Knodell fibrosis score from baseline to week 48. Using the more sensitive Ishak scoring system for fibrosis, which was previously explained to us by Dr. Goodman, which goes from zero for no appreciable fibrosis to 6 for cirrhosis, we examined the change in fibrosis score from baseline to week 48 for each individual patient in Study 437 and 438.

We assumed that a change in fibrosis score of 1 is significant. As shown on this slide, 60 percent of patients in the placebo group in Study 437 had no appreciable change in fibrosis. Approximately 20 percent had improvement in fibrosis and another 20 percent suffered progression in fibrosis.

In those who received adefovir, however, a far greater proportion of patients, 41 percent in the 30 mg group and 34 percent in the 10 mg group had regression of fibrosis compared with only 10 percent who experienced worsening fibrosis.

The differences between the adefovir groups and the placebo groups are statistically significant. This shows that adefovir was therapeutically beneficial in lessening the progression of fibrosis.

[Slide.]

Similar results were also observed in Study 438, which enrolled e-antigen-negative patients. In this study, however, the proportion of patients in the placebo group with worsening fibrosis at week 48 was 36 percent, a figure that is slightly higher than what is seen in the placebo group in Study 437.

With adefovir 10 mg daily treatment, only 4 percent of patients progressed in fibrosis compared with 34 percent showing regression of fibrosis. The differences between the adefovir group and the placebo group again in this case are also statistically significant.

I would like to mention here that these

analyses would have not been possible without the applicant's unprecedented efforts to obtain greater than 90 percent of week 48 liver biopsy.

[Slide.]

Therefore, we conclude with confidence that adefovir treatment had a positive effect on fibrosis, the very process that one would like to control with treatment.

It is also clear that consecutive liver biopsies within a year can detect treatment effect on fibrosis, and it is also worth pointing out here that the use of serum HBV DNA and/or serum ALT as endpoints in the evaluation of drug therapy for chronic hepatitis B will not show this treatment effect.

[Slide.]

We would like to make a few observations on the ranked assessment of liver biopsy previously presented by the applicant.

While it closely reflects the real world liver biopsy examination, this type of assessment is relatively more subjective than the rigid and structured scoring systems.

We also note that the reported results are not completely concordant with those obtained by

the scoring system, and, for example, in Study 438, there were 23 paired baseline in week 48 biopsies with no changes in fibrosis by the Knodell and Ishak scores, however, these were rated as worse than or better than each other by the ranked assessment method.

[Slide.]

We would like to present some pertinent findings on the safety data of adefovir in chronic hepatitis B patients. We will first comment on the adverse events in the two pivotal Studies 437 and 438, and follow with the observations on the renal safety data of these and also Study 235.

[Slide.]

With respect to the adverse event data, we essentially agree with the applicant's assessments. The overall adverse event profile of adefovir groups, particularly the 10 mg group, were comparable to the placebo group.

Additionally, fewer patients in the adefovir group experienced markedly elevated ALT, which is defined as a shift from normal level at baseline to a Grade 3 toxicity level, or from a Grade 1 at baseline to a Grade 4 level of treatment, as shown here.

[Slide.]

Another beneficial effect of the drug was the fact that very few adefovir-treated patients, less than 1 percent, experienced severe hepatic flare compared with 3 percent in the placebo group during treatment.

However, a significant proportion of patients, 35 percent in Study 437 and 47 percent in Study 438 had actually Grade 3 and 4 ALT elevations when they discontinue adefovir treatment, as previously pointed out by Dr. Bhore.

Of these, 3 percent also experienced severe hepatic flare. Now, we also recently received a Medwatch report forwarded to us by the applicant in which a physician described that a chronic hepatitis B patient coinfected with HIV in Study 423, which is the adefovir extended access program, died of hepatitis flare a month and a half after discontinuation of adefovir.

[Slide.]

I would like to present a summary of our findings on the renal safety data of Studies 437, 438, and particularly 435. Some of these findings have been previously presented by the applicant.

We based our analysis on the confirmed

increase from baseline in serum creatinine and/or decrease in serum phosphorus. A confirmed change is made only when two consecutive measurements of these laboratory parameters, frequently two visits one month apart, were abnormal.

For a serum phosphorus, we set the threshold at a decrease to less than 2 mg/dL, that is, a Grade 2 toxicity or higher since oral phosphate supplement is often given when a patient had persistent hypophosphatemia of this degree.

For a serum creatinine, in Studies 437 and 438, we will show the data using the cutoff of greater than or equal to 0.3 mg/dL increase from baseline. In Study 435, we will use both cutoffs 0.3 and 0.5.

[Slide.]

The rationale for selecting an increase in serum creatinine from baseline of 0.3 or higher in our data analysis of Studies 437 and 438 is as follows.

Patients in Study 437 and 438 essentially had to have normal serum creatinine at baseline to be eligible for enrollment. The mean baseline serum creatinine values for these patients are shown on this slide, approximately 0.9 for men and

0.6 for women.

In a typical male or female patient with an average weight and average age as a patient in these studies, an increase of 0.3 mg/dL in serum creatinine would represent approximately 25 percent or 33 percent respectively.

Now, choosing a cutoff of 0.5 or greater would mean that a typical male or female patient in these studies would have had treatment emergent nephrotoxicity resulting in a loss of approximately 35 to 45 percent of renal function respectively before the toxicity was detected. Such a threshold, in our opinion, would be unacceptably high.

[Slide.]

In the first 48 weeks of Study 437, approximately 40 percent of patients in the adefovir 30 mg group and 4 percent in the adefovir 10 mg group compared to less than 1 percent had confirmed increase in serum creatinine, while up to 77 percent of the affected patients in the adefovir group had resolution of serum creatinine to less than or equal to 0.2 mg/dL, half of them actually following a dose reduction of adefovir to 5 mg.

The majority of those affected in the 30

mg group did not. Five percent of patients in the adefovir 30 mg group and none in the 10 mg group compared with 1 percent in the placebo group had clinically significant hypophosphatemia. Among those affected in the 30 mg group, 67 percent required oral phosphate supplementation.

As we understand it, the applicant did not seek further drug development with the adefovir 30 mg group, 30 mg daily dose, because of these very toxicities.

[Slide.]

In the first 48 weeks of Study 438, a slightly higher proportion of patients in the placebo group, that is, 5 percent, experienced increase in serum creatinine compared with 3 percent in the adefovir 10 mg group.

The 3 percent here was comparable to that observed in Study 437. While the numbers are small, we note that only 2 out of 5 affected patients had resolution of the creatinine abnormality. Again, no patients in the adefovir 10 mg group had confirmed hypophosphatemia Grade 2 or higher.

[Slide.]

By week 96 of the study, approximately 9

percent of patients in Study 437 and 10 percent in Study 438, mind you that the patients in Study 437 were those on adefovir 10 mg daily dose, developed an increase from baseline in the serum creatinine of 0.3 or more by Kaplan-Meier estimate.

Due to the study design, no placebo control data were available beyond week 48 for comparison purposes.

[Slide.]

Let us turn to Study 435. This study, as you recall, is an open-label study of adefovir 10 mg dose, or in some cases, 5 mg dose, in chronic hepatitis B patients with lamivudine-resistant hepatitis B virus.

The patient population was divided into cohort A, which included patients status post liver transplantation, and cohort B, which included patients on the waiting list for a liver transplant.

Now, these cohorts were further subdivided into sub-cohorts 1A, 1B, 3A, 3B for patients with adequate or inadequate renal hepatic and/or hematologic functions at baseline.

Now, adding to the complexity a few patients who had received adefovir treatment in

another study were also enrolled into sub-cohort 2A and 2B.

Now, the analysis of nephrotoxicity in this study was complicated by multiple factors - the uncontrolled study design, the advanced liver disease status particularly in patients of cohort B, a number of liver transplantations that occurred in cohort B patients while the patients were on the study, the concomitant use of nephrotoxic immunosuppressive drugs primarily in cohort A patients, the underlying renal insufficiency in cohort A patients, and the paucity of data after week 48 of the study.

[Slide.]

For this study, we will show renal data analysis based on serum creatinine cutoff of 0.3 and 0.5, as I mentioned previously. The number of patients in subcohorts 2A and 2B were relatively small, and the results for subcohorts 1A, 1B, 3A, 3B were quite similar, hence, we elected to show composite data for cohorts A and B only.

As you can see on this slide, cohort B patients essentially had normal serum creatinine at baseline. In fact, only 5 percent had baseline serum creatinine of Grade 1 or higher, that is,

greater than 1.5 mg/dL. In contrast, cohort A patients had relatively higher baseline serum creatinine values as indicated by the mean serum creatinine of 1.3 in men and 1.1 in women.

Although these values were still considered within normal limits, they were not inconsequential since they indicate a certain degree of pre-existing renal dysfunction.

As you already know, serum creatinine may not rise to levels beyond the range of normal despite a loss of as much as 50 percent of renal function.

Now, at 0.3 mg/dL increase from baseline, in a typical male patient in cohort A with average age and weight as one in the study, would represent an additional loss of 18 percent renal function on top of the pre-existing insufficiency.

For a typical female patient, it will be 22 percent additional loss. Likewise, you see here the degree of additional renal function loss calculated for cutoff value of 0.5 mg/dL increase in serum creatinine.

[Slide.]

As shown in this slide, the Kaplan-Meier analysis showed that in cohort A, that is, patients

status post liver transplantation, approximately 26 percent of them had confirmed increase from baseline in serum creatinine of 0.3 or higher by week 48 and 37 percent by week 96.

In cohort B, that is, patients on the waiting list for liver transplantation, up to 30 percent of patients had increase of serum creatinine by week 48 based on Kaplan-Meier estimate.

The data for this cohort unfortunately were insufficient to estimate the figure for week 96.

As you will recall, only 4 percent of patients in the pivotal studies who received the same adefovir 10 mg daily dose had similar serum creatinine abnormality of 4 percent by week 48 and 10 percent by week 96.

More patients in this study had clinically relevant hypophosphatemia than those pivotal studies, that is, 4 percent by week 48, 6 percent by week 96 for cohort A and 5 percent by week 48 for cohort B patients.

[Slide.]

Now, if the cutoff value of 0.5 or greater is used, the proportion of patients with increase

in serum creatinine would naturally be lower, as shown in this slide. By Kaplan-Meier analysis, 9 percent of patients in cohort A developed this abnormality by week 48 and 23 percent by week 96, compared to 19 percent in cohort B by week 48.

Now, we should look closer to the 28 percent in cohort A and 15 percent in cohort B.

[Slide.]

Of the 28 patients in cohort A who had serum creatinine increase greater than 0.5 mg/dL from baseline, 100 percent were actually taking concomitant nephrotoxic immunosuppressive drugs. Seventy-one percent of these patients had renal dysfunction at baseline as indicated by creatinine clearance less than 80 mL/min.

Of the 15 patients in cohort B who had similar abnormality, only 4 or 27 percent had renal dysfunction at baseline. However, we note that 12 of them or 80 percent of these patients experienced abrupt increase in serum creatinine shortly after undergoing liver transplantation, and a number of them, in fact, had post-op complications including acute renal failure.

Subsequently, all of these 12 patients were placed on immunosuppressive drugs, therefore,

we did not believe that the acute renal insufficiency in these patients was mainly due to adefovir-induced nephrotoxicity.

[Slide.]

Now, let us look at the data on resolution of serum creatinine abnormality in these patients using an arbitrary value of serum creatinine returning to less than 0.3 mg/dL as a marker.

As shown in this slide, the majority of patients, 86 percent in cohort A and 80 percent in cohort B, did not achieve resolution by the last follow-up visit, that is, the serum creatinine remained persistently elevated.

Again, we need to keep in mind the patients in cohort B, that 12 out of 15 of these patients had one or more acute clinical events and insults that led to the renal compromise and in which adefovir probably plays a very minor contributory role.

[Slide.]

Now, we did a case-by-case review of these patients. Although we were very keenly aware of the confounding factors as listed on this slide, we were unable to completely rule out the contributory role of adefovir in 22 out of 26 cases in cohort A

and 2 out of 15 cases in cohort B.

In Appendix B of the FDA briefing document, we have attempted to provide you with some typical examples of cases in which the contributory role of adefovir was probably none to minimal.

We also included some typical cases where adefovir probably had a larger contributory role in the patient's deteriorating renal status.

[Slide.]

One of these cases is illustrated on this slide. The patient was a 69-year-old man status post liver transplant in 1995. he started adefovir 10 mg daily in April of 2000. The concurrent medications were noted for cyclosporine and lamivudine, I guess for lamivudine- resistant hepatitis B virus. The notable laboratory results are shown here.

It is clear that the patient had underlying renal impairment at baseline with a creatinine clearance of approximately 51 mL/minute or about half of the expected normal values.

The patient's serum creatinine did not appreciably increase until December of 2000 or approximately 8 months into adefovir treatment. It

was not until when the serum creatinine peaked at 2.2 mg/dL and creatinine clearance was reduced to essentially 37 mL/minute in August of 2001, that adefovir was interrupted and restarted at a lower dose of 5 mg.

Four months later, in January of 2002, the serum creatinine did not appear to decline. This was a typical case in which we could not confidently rule out the contributory role of adefovir to a patient's decline in renal function.

[Slide.]

Let me bring up another example of a more complicated case. The patient was a 65-year-old male, status post liver transplant back in 1999. He started adefovir 10 mg in November of 1999. The concurrent medications were again noted for lamivudine since he harbored lamivudine-resistant hepatitis B virus, cyclosporine, sirolimus, furosemide, and antihypertensives. The relevant laboratory data are again listed there.

This patient also had significantly underlying renal insufficiency with a creatinine clearance of 40. Within three months of adefovir treatment, the serum creatinine began to rise, and by May of 2000, the serum creatinine was 3.0 mg/dL

and the creatinine clearance was significantly reduced to 25 mL/minute.

At this point, the adefovir dose was reduced to 5 mg. In August of 2000, three months later, the serum creatinine still remained elevated at this level. In late November of 2000, the patient was hospitalized with signs and symptoms consistent with hepatorenal syndrome, which also required renal dialysis.

The patient subsequently died of aspiration pneumonia complicated by hepatic and renal failure in I believe late December 2000.

Again, in this case, we could not rule out the contributory role of adefovir in the patient's progressive renal deterioration after commencing adefovir treatment, however, it is unclear as to whether there was an association between adefovir treatment and the hepatorenal syndrome that occurred in November of 2000.

[Slide.]

Now, we had the benefit of hindsight in the course of the review when the pharmacokinetic data of Study 473 became available. Now, this was a study to evaluate the pharmacokinetic parameters of adefovir single dose in non-chronic hepatitis B

patients who had various degrees of renal dysfunction.

The results of this study are summarized here for your information. As you can see, patients with moderate to severe renal dysfunction, whose creatinine clearance was less than 50 mL/minute, had significantly greater exposure to adefovir than those without.

In fact, the concentration of adefovir in patients with creatinine clearance of less than 30 mL/minute were as high as what is seen in the HIV program with adefovir dosed at 60 to 125 mg daily.

The two patients mentioned previously perhaps had plasma adefovir concentration twice as high or more than is intended. Based on these results, we began more concerned that adefovir at the 10 mg daily dose was probably not the optimal dose for chronic hepatitis B patients with underlying renal insufficiency, but for these very patients, particularly those who harbor lamivudine-resistant hepatitis B virus, adefovir may be the only treatment available.

[Slide.]

At present, the pharmacokinetic data for adefovir in chronic hepatitis B patients with

underlying renal dysfunction are unavailable, however, extrapolating from the results of Study 473 mentioned previously, it appears that adefovir 10 mg daily dose may result in significantly higher plasma levels in these patients than those with intact renal function as in the two pivotal studies.

As pointed out in its presentation, the applicant is planning to conduct a study to evaluate various adefovir dose modifications in these patients based on the patient's baseline serum creatinine clearance using the 10 mg strength tablet.

The dose modifications, however, we believe could be further optimized if a lower strength formulation of the drug is available.

[Slide.]

We now move on to mention that there were four deaths, three in Study 437 and one in Study 438. These deaths occurred after the clinical data cutoff date or after completion of the 96 weeks of study drug.

In Study 435, as of the data cutoff date, there were 18 patients in cohort A who died and 24 in cohort B who died.

Now, in two of these cases, 1 in cohort A and 1 in cohort B, the patient exhibited a pattern of nephrotoxicity temporally compatible with that induced by adefovir. The former case, in cohort A, was the second example that we cited previously.

These cases and other notable cases have been summarized in our FDA briefing document for your information.

[Slide.]

I would like to briefly comment on some viral resistance issues. First, we note that the genotypic analysis of DNA sequences from clinical specimens may not be able to detect viral variants present at less than 30 percent in a mixture of viruses.

Furthermore, it has been observed that resistance is slow to develop, slow to emerge during the treatment of hepatitis B virus. Therefore, it is possible that adefovir-resistant mutants may emerge during longer term treatment, that is, longer than 48 weeks.

[Slide.]

In Study 437, we note that the IC50 of H582Q, a mutant of the conserved site of the viral polymerase, found in a patient who received

adefovir 10 mg daily was approximately 3.6-fold higher than that of the wild-type virus by in vitro assay.

Nevertheless, the patient exhibited profound viral suppression as evidenced by close to 6 log HBV DNA reduction at week 48. Therefore, it is unclear as to the clinical significance of this shift in susceptibility.

Again, in Study 437, there were two patients with polymorphic site substitutions listed here, the E349E/Q, K487K/N, who had suboptimal virus suppression at week 48, that is, minus 1 and minus 3 log of serum HBV DNA respectively at week 48.

These two patients had no drug compliance issues. Now, according to the applicant, however, patients with 349E/Q and 487/N mutants at baseline had, in fact, comparable viral suppression by adefovir as in wild-type virus. Therefore, it is unclear to us as to why these two patients had suboptimal viral suppression.

In Study 460i, which is an open-label study to evaluate adefovir 10 mg daily dose in HBV/HIV co-infected patients with lamivudine resistant-hepatitis B virus, one mutation, R462G,

occurred--this is a mutation in viral polymerase--occurred in relatively high frequency, that is, 7 out of the 20 patients with available genotyping data.

However, only 1 of these 7 patients had suboptimal viral suppression at week 48 compared with the other 6.

Again, it is not clear whether this mutation is or is not clinically significant at this time.

We also note that 2 of the 20 genotyped patients had a substitution at N470 T or L.

[Slide.]

Historically, in vitro selections produce 2 adefovir-resistant HIV mutations, K65R and K70E. These mutations cause a 12 to 16 and 9-fold in vitro resistance to adefovir respectively.

Only the K70E has been observed clinically with reportedly no loss in HIV RNA suppression. In Study 460i, there were 13 patients with available HIV reverse transcriptase genotype data. None of these patients harbored the K65R or the K70E mutation.

There were 5 patients with zidovudine or d4T-associated mutations, and lastly, all the

patients had persistent M184V mutation. This is the lamivudine-associated HIV mutation at baseline and week 48.

[Slide.]

In the next two slides, I will summarize our risk-benefit assessments of adefovir for the treatment of chronic hepatitis B patients.

Compared with placebo, treatment with adefovir 10 mg daily dose resulted in the following benefits: Improvement in liver biopsy histology at week 48, suppression of wild-type and lamivudine-resistant hepatitis B virus, albeit data in the latter were limited.

Improvement in transaminases during treatment. Higher e-antigen seroconversion rate. Lower incidence of significant ALT and AST elevations and hepatic flare during treatment.

No definitive adefovir-associated resistance mutation identified by week 48.

[Slide.]

We observed that with respect to the adefovir 10 mg daily dose, the risk of nephrotoxicity in chronic hepatitis B patients with intact renal function and compensated liver disease was relatively low by week 48.

The risk, however, increased with longer duration of treatment in these patients, as I have previously shown. However, in patients with pre-existing renal dysfunction, we are concerned that the nephrotoxicity risk may be substantial unless dose of adefovir is modified.

The applicant has proposed a dose modification scheme in these patients, however, the pharmacokinetic safety and effectiveness data, as such, are not yet available.

Last, but not least, there is a potential serious flare or exacerbation of the disease associated with drug discontinuation.

With these and the information presented by the applicant, we would like to present the committee the following questions, and I would ask for permission to read them off.

[Slide.]

The first question. Has the applicant demonstrated the safety of adefovir 10 mg daily dose for the treatment of chronic hepatitis B patients?

We would like you to discuss the safety of adefovir in patients with decompensated liver disease and patients with renal dysfunction at

baseline.

The second question. Has the applicant demonstrated the effectiveness of adefovir 10 mg daily dose for the treatment of chronic hepatitis B patients?

In the discussion, please comment on the effectiveness of adefovir in patients with compensated liver disease, decompensated liver disease, lamivudine-resistant hepatitis B virus, presumed precore mutation, and HBV/HIV coinfection.

[Slide.]

The third question. Based on the risk-benefit profile, does the committee recommend approval of adefovir 10 mg daily dose for the treatment of chronic hepatitis B patients in adults?

The fourth question. Are there any issues with the safety and effectiveness data that should be highlighted in the drug label? That is, if you vote yes on 3.

In particular, please discuss the use of adefovir in HBV/HIV coinfection and the potential risk of inducing NRTI resistance.

The last question. Please recommend appropriate Phase IV postmarketing studies for

adefovir in chronic hepatitis B patients.

In this discussion, please comment on the adequacy of the applicant's current program to detect the emergence of adefovir-resistant hepatitis B virus and the optimal strategy for long-term resistance surveillance.

With that, I would like to sincerely thank and acknowledge the dedication, collective efforts, and valuable contributions of my colleagues on the FDA review team to make this presentation possible, and on behalf of the FDA review team, I would like to extend to the many members of Gilead Sciences, particularly Dr. Brosgart, for her tremendous patience and assistance in providing the data for our review, and thank you very much.

DR. GULICK: We are going to open this to the committee for points of clarification or specific questions. Just to remind the committee members, we will have time to address the questions presented to us in the afternoon session, so let's try to focus on clarifications and questions for either the sponsor or for the agency.

Dr. Wong will lead us off.

Discussion of Presentations

DR. WONG: I guess I really have two

questions to the sponsor, and they both relate to the potential nephrotoxicity.

The first is that the data that you presented here today seemed different from the data that was in your briefing book in Table 13. Table 13 on page 44 of the briefing book showed that creatinine increased in 1 of 228 placebo recipients, 7 of 294 recipients of adefovir 10 mg from zero to 48 weeks, and 9 of 492 adefovir recipients, 10 mg, from zero to 96 weeks, and then the data that you showed in Slides 38 to 40 seemed to show considerably lower proportions than that.

So, I guess I would just ask that you reconcile those and tell me why the difference.

Then, the second question is a little bit different. I think I got the answer from Dr. Nguyen's presentation, but I guess I would like to hear your information on this, too.

When you proposed this dose reduction strategy, what you didn't tell us is how many people who had these various degrees of renal insufficiency actually received those reduced doses and how did those patients do with respect to either resolution of their renal insufficiency or development of further renal insufficiency.

Really the question is, is this strategy based on the pharmacokinetics mostly or is there, by this time, a real database of experience for safety of this scheme, or is that all in the future.

So, those are really the two questions.

DR. GULICK: Before you answer, Dr. Wong, can you remind us again the page that you were referring to and the slides you were referring to.

DR. WONG: The slides were Slides 38 to 40, and the page in the briefing book that I was concerned about the differences in the data was Table 13, page 44, and the line was the line that totaled up patients in whom creatinine increased.

DR. GULICK: Thanks.

DR. BROSGART: Dr. Wong, could you just give me the table number in the Backgrounder that you were referring to?

DR. WONG: It's Table 13, page 44, number of patients with related adverse events, and then eight or nine lines down, it is the number of patients in whom creatinine increased, and reading across, the placebo group 1 out of 228, adefovir 10 mg zero to 48 weeks, 7 out of 294, and then all adefovir 10 mg zero to 96 weeks, 9 of 492.

DR. BROSGART: Yes, I can answer that for you. What you are looking at are adverse events, not laboratory abnormalities, so if a patient had a change in creatinine, even if it didn't meet a graded change or even if it didn't meet the protocol-defined limit of toxicity, the physician could report it on the adverse event case report form.

Early on in the first year of the Study 437, we initially employed sort of a two-step toxicity management strategy. If a patient had a 0.3 to 0.4 confirmed increase in serum creatinine, we recommended dose reduction in a blinded fashion, so a patient on 30 mg would have been dose reduced to 10 mg, the patient on 10 mg, to 5, and a placebo patient would get placebo.

After meeting with the agency in April of 2000, after we were beginning to see, in a blinded fashion, we didn't know which treatment arm this was occurring, but we were seeing the need for dose reductions, and we were seeing renal laboratory changes, both at the 0.3 and the 0.4, and at the greater or equal to 0.5 range.

In discussing this with the agency, and we had seen changes at the 0.5 level in a Phase II

extended dosing study with 30 mg, the agency recommended, and we concurred, and we later presented this to our Data Monitoring Committee, and they concurred, that having a dose reduction strategy would complicate the assessment of incidence of nephrotoxicity.

So, we discontinued any dose reductions at the 0.3 or 0.4 level, and instead, modified the protocol for patients to be permanently discontinued from study drug if they developed a 0.5 change in serum creatinine by eliminating any dose reductions for more minor changes.

We felt that we would then see a truer incidence of nephrotoxicity at either dose, and have a truer evaluation of resolution.

So, when you are looking at these cases, then, in Table 13, if a physician did have a patient who had a 0.3 or a 0.4 change, and they happened to be in the placebo arm that could have been recorded as an adverse event, and would not have appeared as a--this was not a 0.5 mg/dL change. So, that is why these numbers don't correlate with the renal laboratory abnormalities.

DR. WONG: And the second question?

DR. BROSGART: I was just going to come to

the second part of your question.

We conducted a pharmacokinetic study in patients with varying degrees of renal impairment including patients on dialysis. These were in patients with renal impairment, I wouldn't call them healthy, but they were not hepatitis B chronically infected.

It was from that study using adefovir 10 mg that we were able to show that when creatinine clearance is less than 50 mL/minute, there is increased adefovir exposure. It is from that study that we have now made our dose interval guidelines, and that is what we have recommended in the proposed package insert.

The patients who were in the transplantation study were not managed according to those dosing interval guidelines until just recently. Those results have just become available.

We have amended that protocol, and now patients currently enrolling in the transplantation study, moving forward, will be dosed initially according to those dosing guidelines, and patients who have creatinine clearance abnormalities at this time have been now dose adjusted, but the data you

saw matured on a different dosing strategy.

Given that many of these patients in the study were dosed differently, we are beginning a new study, Study 526, which will prospectively evaluate, in a long-term safety and efficacy study, the dose interval strategy in patients who have chronic hepatitis B and varying degrees of renal impairment, and we will be able to then assess in those patients whether or not 10 mg with an interval modified according to creatinine clearance provides efficacy for the underlying hepatitis B disease and also provides a greater measure of safety in that population.

DR. WONG: So, if I understand correctly, you have no data at this point on that point.

DR. BROSGART: We don't have data that has emerged yet, that is just beginning. Our data that predicts the appropriate dosing interval comes from the pharmacokinetics study.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: I had two somewhat unrelated questions. The first one relates to the relationship between viral load and histologic improvement, and specifically, were there patients who had sustained suppression less than 400 copies

DNA, who failed to show histologic improvement at 48 weeks.

DR. BROSGART: If you can just give me a minute, Dr. Mathews and we will pull that up for you.

[Slide.]

This will demonstrate the histological improvement by the HBV DNA response. On the lefthand side is the e-antigen-positive study, Study 437. On the righthand side of the screen, the e-antigen-negative study, Study 438.

In this analysis, we are looking at patients in three categories. Too many more categories and it wouldn't have fit on the slide. So, we looked at patients who become undetectable less than 400 copies/mL.

The next interval is patients between 400 copies and 100,000 copies, and then the last are patients who are greater than 100,000 copies. The adefovir 10 mg patients demonstrated in yellow, and placebo patients in gray, you will see that of the adefovir 10 mg patients in the e-antigen-positive study, who achieved an undetectable HBV DNA less than 400, 72 percent of them had histological improvement.

There were no patients in either the e-antigen-positive study or the e-antigen-negative study who achieved an undetectable serum HBV DNA, so there are no patients in that category.

If you then look at the 400 to 100,000, you will see that again there is a treatment benefit for adefovir with 59 percent of those patients in that category, with that HBV DNA response at the week 48 visit having improvement compared to 41 percent of the placebo patients.

Then, looking at those patients greater than 100,000 copies/mL, 40 percent of the adefovir patients have improvement, 24 percent of the placebo.

So, there appears to be a correlation with the HBV DNA response, although not a complete correlation in the e-antigen-positive study.

When we look at the e-antigen-negative study, it is not the same. You don't see the same trend. You do see that 64 percent of the patients whose HBV DNA is less than 400, of the treated patients, show histological improvement, and again there is no one in the placebo group, but 75 percent of the patients in the 400 to 100,000 range show histological improvement, so actually more

patients at that little bit higher viral load range showing improvement compared to those patients who were undetectable.

Yet, when we look at the patients whose HBV DNA at week 48 is greater than 100,000, you see that 77 percent. So, there is not a good fit for the change in HBV DNA with the histological response at week 48.

This is showing it in a very visual way. Our statisticians have been working in a much more mathematical way, looking at whether or not HBV DNA is a good or a complete surrogate, and while it appears to be, well, not a complete surrogate, a better surrogate in the e-antigen- positive, it appears to be a poor surrogate in the e-antigen-negative patients.

We have been working with the agency, who have been doing similar analyses with our data and also with other datasets, and this is going to be the topic of tomorrow's special Advisory Committee on endpoints in hepatitis B clinical trials, but it would appear that change in HBV does not completely explain histological response, but in some populations, we do see a correlation.

DR. MATHEWS: If you focus just on the

ones that were less than 400 copies, you showed us the percentage that did not improve, what percent actually worsened even though they were not detectable by that assay?

DR. BROSGART: Let me pull that up.

DR. MATHEWS: The reason I am asking this, what you are alluding to, one of the questions the committee is going to be dealing with tomorrow is to what extent biopsies are necessary in future trials.

DR. BROSGART: Right.

[Slide.]

I think your question came from this slide, Dr. Mathews, where you saw that 13 percent of e-antigen-positive patients and 3 percent of the e-antigen-negative patients were perceived to have worsened in the ranked assessment.

DR. MATHEWS: But specifically the group that had sustained virologic suppression.

DR. BROSGART: Let me just pull up that data, if you can give me just a minute.

I am going to have to come back to you with that either a little bit later this morning or this afternoon because I don't have the data with me broken out by their viral load change

completely, so we will come back to that later.

DR. MATHEWS: Okay. Could I ask one other question?

DR. GULICK: Sure.

DR. MATHEWS: Were there patients, well, I assume there were, who had virologic rebound after initially becoming undetectable during the first 48 weeks?

DR. BROSGART: Right.

DR. MATHEWS: Because when you presented the resistance analyses, that was starting out with looking for mutations and then looking at their virologic response. When you turn it the other way around, what proportion of people actually had virologic rebound, and if resistance wasn't the reason for it, what are your thoughts on what happened to those types of patients?

DR. BROSGART: We had two approaches in our resistance surveillance program. One was the active surveillance based on looking at change from baseline genotype and correlating that, if there were substitutions, with phenotypic and the clinical responses.

In addition to that, as part of our prospective virology protocol, we included an

evaluation for patients who demonstrate viral rebound. The definition that we used, we used a rather broad definition because we didn't know going into these studies, what the correlates of resistance could be.

So, we threw a very wide net and used a definition, which was that if we saw an unconfirmed 1 log increase in serum HBV DNA from the on-treatment nadir, we would then do additional resistance evaluations.

So, we have gone ahead and done that, and all cases of rebound have been analyzed both clinically and virologically, and there was no evidence of adefovir-associated resistance in any patient who had an unconfirmed, 1 log increase from their on-treatment nadir.

DR. MATHEWS: So, why did they rebound?

DR. BROSGART: Well, I can show you. Hold on.

[Slide.]

So, these are all of the patients from the integrated dataset from Study 437 and 438 for the first year analysis. There are 294 patients from the randomized arm of either Study 437 or Study 438 who were treated with adefovir 10 mg.

Of those, there were 24 patients who had this greater or equal to 1 log unconfirmed increase from nadir at week 48 or at their last visit, so 24 patients. We then have looked in the database and at the CRF records for were there any adherence issues, treatment interruptions, treatment discontinuations, missed visits that could explain the unconfirmed change in viral load, and there were adherence issues identified in 18 patients.

There were no adherence issues identified at least in what was in the database in 6 of these patients. We have not gone out to the sites to look at the actual clinic charts, so this is just coming from the case report form data.

Of the 18 patients who did have adherence issues, when they were genotyped, 2 of them were without any substitutions, I think 2 of them did have substitutions although these were not conserved site substitutions, these were polymorphic substitutions, and there were 16 patients who had no substitutions in the HBV DNA polymerase.

If we then go to the far side of the slide looking at the 6 patients for whom we were not able to identify any adherence issues, there were 2

patients who had substitutions. These were polymorphic substitutions, not substitutions at conserved sites, and there were 4 patients without substitutions.

[Slide.]

Let me now show you the susceptibilities from the patient-derived recombinant HBV to adefovir in cell culture. Those are the patient numbers on the far left. You can see the individual polymorphic substitutions.

The next column is the IC50 in micromoles at baseline, and the IC50 at week 48. Then, the last column is the fold change, so there is not an appreciable fold change from baseline in these 4 patients. So, this does not explain the transient viral rebound.

[Slide.]

Going back to the previous slide, for the remaining 4 patients for whom we did not identify adherence issues, phenotypic analysis is ongoing.

DR. GULICK: Dr. Kumar.

DR. KUMAR: Dr. Brosgart, I have three questions for you. First, by looking at all the datasets, would you comment for a clinician, at what point could you say if a patient, the hep-B

viral load is not coming down, that they are not going to respond to treatment, by which week can you say if it has not come down, it is not going to come down?

DR. BROSGART: What you are really asking is are there patients that we have identified who are non-responders in terms of response to HBV DNA.

DR. KUMAR: And also by which week can a clinician not continue to expose them to adefovir that they are not going to respond to?

[Slide.]

DR. BROSGART: We define virologic non-response as a less than 1 log decrease in serum HBV DNA by week 16. With this definition, and this is now looking at all of the adefovir-treated patients from both Studies 437 and 438, so the adefovir 10 mg arms is from both studies, the 294 patients plus the 173 adefovir 30 mg patients, using that definition, we identified 2 non-responders amongst the 467 adefovir patients. That should be 30 mg and 10 mg up on the slide.

One of these was in adefovir 10 mg and one of these was in adefovir 30 mg. The adefovir 30 mg patient, though, had discontinued drug at week 16, so he was not really a true non-responder.

In the adefovir 10 mg patient, I will show you that patient plot in just a minute, we then did go ahead and do genotyping, and there were no conserved site substitutions in the baseline HBV isolate for this individual patient.

Let me just have that second slide.

[Slide.]

So, this would show you, this is the 10 mg patient for whom we did not see at least a 1 log decline in HBV DNA confirmed at week 16. We now have a new technique where we are able to, in addition to doing genotyping, actually clone the entire genome for this patient, so we are in the process of doing that, that phenotypic analysis is ongoing. We will have a better idea after we take a look at that phenotypic analysis.

To date, we have not identified any individual mutations or groups of mutations that are associated with non-response to adefovir, but part of our surveillance program is not only to identify substitutions that are treatment emergent that could confer resistance, but to try to see whether there are mutations that exist in chronic hepatitis B patients that might confer decreased susceptibility even at the time of initiation of

therapy.

DR. KUMAR: Can I just rephrase the question. By week 16, if a patient's hep-B viral load has not come down, can a clinician at that point say that that patient is unlikely to respond to adefovir?

DR. BROSGART: Well, HBV DNA has yet to be validated as a surrogate, as a complete surrogate in the treatment of patients with chronic hepatitis B, and from the data that I showed a little earlier in response to Dr. Mathews, it does explain some of the treatment response in the e-antigen-positive patients, but it is a poor predictor of response in the e-antigen-negative patient.

I don't think we truly have a complete understanding of all of the correlates of treatment response or what are the surrogates, and one would have to look at the whole patient and see whether or not there are other parameters, is there an ALT response, if it's a symptomatic patient, are symptoms going away, if it's a decompensated patient, has there been improvement in other clinical efficacy parameters, but I think to focus only on HBV DNA would be difficult because it doesn't have the same clinical meaning yet, and may

never, in the treatment of chronic hepatitis B patients that HIV RNA does in the treatment and the management of HIV patients.

DR. KUMAR: In your study, the hepatitis B e-antigen patients, I think 12 percent of your patients had seroconversion, they lost the e-antigen and developed an e-antibody.

In what percent of that 12 percent, when they stop adefovir, did they have a viral rebound?

DR. BROSGART: All of those patients who seroconverted have sustained their seroconversions, and those patients have had a median follow-up, well, I was right, I was going to say 64, and it is 64.

So, of the patients who seroconverted in Year 1, the first 48 weeks of study, 11 of the patients were then re-randomized to continue adefovir 10 mg, 9 of those patients were re-randomized for the second year to discontinue adefovir 10 mg.

One of our goals of study, not only in looking at the safety of discontinuing therapy, but also was to be able to evaluate is seroconversion durable. The median follow-up in these two groups ranges from 64 for the patients, 64 additional

weeks of follow-up after week 48 in the patients who continued on 10 mg, and it was 72 weeks in these patients who discontinued at week 48.

One hundred percent of the patients who continued on adefovir 10 mg sustained their e-antigen seroconversion, and 100 percent of patients who discontinued after 48 weeks of therapy were able to sustain their seroconversion.

We are not stopping there, though. We have a long-term safety and efficacy study evaluating the durability of seroconversion, Study 481, and the patients from our e-antigen-positive study who have seroconverted either during Year 1 or Year 2, or if patients seroconvert later in our long-term safety and efficacy study, is continuing in 437 and 438, those patients are all being rolled over into the durability of seroconversion study.

Three years from now, we will be able to say what is the 5-year durability of seroconversions, but at least at 1 to 1 1/2 years, it appears to be durable.

DR. KUMAR: My final question. Your briefing document, and the agency had also pointed out, that only 3 persons in the patient enrollment were African-American. Would you shed some light on

those numbers, is it that those sites just had fewer African-Americans, did they have more exclusion criteria, could you just shed some light on that?

DR. BROSGART: Getting a good handle on the demographics of chronic hepatitis B in the United States has been a real challenge, not only for us, but I think also for the agency.

As you look at the data, there is a lot of data from the Centers for Disease Control on incidence of acute infections, and certainly the incidence of acute new infections of hepatitis B are more common in adult Blacks in the United States, but the chance of becoming chronically infected when one acquires hepatitis B infection as an adult is low, and generally, 95 percent of adults clear those infections.

So, when you look at the CDC data on incidence and prevalence for acute hepatitis B in the U.S. in adults, it doesn't give you a good handle on how many patients have chronic hepatitis B and are seeking care for their chronic hepatitis B.

Patients who are seeking care for chronic hepatitis B may have acquired it in adulthood

although the majority of patients who have chronic hepatitis B in care have acquired it as part of childhood or vertical transmission.

When we look in the clinic populations, many of those patients, in fact, are Asian, so in looking at the e-antigen-positive study, which is the study that enrolled in this country, it was two-thirds Asian, and that was pretty consistent across study sites. That wasn't just coming from the Asian sites.

We are hoping that some of our newer and further studies that are being conducted in special populations and plus some of the new initiatives we are taking will allow us to gain more safety and efficacy data in a broader range of patient populations. Certainly, our coinfection studies being conducted within the AIDS Clinical Trial Group, the demographics of those patients in studies are broader than the demographics in our group.

But some of the data that were shown, that was in the Backgrounder or in the agency's presentation, that came from the NHANES dataset, and I think you will notice that it completely left out Asians, and yet if you speak to any of the

hepatologists who are either sitting on the committee or have come with us today from Gilead, the hepatology clinics around the country are filled with Asians, and that reflects the incredible immigration pattern to the U.S. particularly since the mid-seventies.

So, I don't think anyone has a good handle on what the exact demographics are within hepatitis clinics throughout the country, but we are going to work to enroll more patients, both Blacks and Hispanics, but we did have considerable experience in the adefovir for HIV program, and, in fact, in that program, 1,400 of our patients were Black, and I believe it was close to 1,000 were Hispanic, so certainly at the higher doses of 60 and 120 mg, we had considerable experience in other ethnic groups in this country, and we did not see an increased incidence of nephrotoxicity, which would be the biggest I think concern particularly given some of the issues in the Black American population with hypertension and risk for a variety of reasons, the risk for renal disease.

We actually saw a lower incidence of adefovir-related nephrotoxicity in the HIV program in Black HIV infected patients as compared to

Caucasian HIV-infected patients.

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

DR. WOOD: I would like you to just make a note regarding the FDA's presentation of the PK's in patients with non-chronic hepatitis B, and the fact that the creatinine clearance of less than 30 is associated with severe exposure associated with equivalent doses of 60 to 120.

So, I would just suggest that in Slide 65, the dosing recommendations for the interval dosing of adefovir kind of be correlated with that, because as it is right now, referring to Slide 65, patients, the first dose reduction would be for patients from 20 to 49, and then there are two different dosing levels from 10 to 19 in terms of mL/minute and less than 10, but in essence, based on your PK studies, everyone who is less than 30 would have potentially severe exposure to adefovir.

The questions that I had specifically were I didn't have a sense of out of the 437 and 438 studies, what percentage of patients actually required a dose reduction in adefovir, and then once they were dose reduced, what the efficacy data looked like, not from a toxicity standpoint, as Dr.

Wong was addressing, but really in terms of what their outcomes were as far as histopathology, HBV DNA responses, that kind of thing.

DR. BROSGART: I think there were a couple parts to your question, and the first part was going back to the dose interval guidelines and why the dose interval guidelines don't match the same buckets of creatinine clearance.

We did our pharmacokinetic study according to standard ICH guidelines, and in that, we had different groups of patients, patients with normal renal function greater than 80 mL/minute, patients who had creatinine clearance between 50 and 80, patients who were between 30 and 50, patients who were less than 30, and then patients who were on dialysis.

When we evaluated the data, we found that for patients who were greater than 80 mL/minute--why don't we take away Slide 65 and bring up the next slide--so those were the categories that we evaluated.

[Slide.]

When we looked at the patients with normal renal function or the patients with mild impairment, the adefovir exposures were similar and

wouldn't warrant a change in dose.

When we looked at the patients between 30 and 49, and then less than 30, we found that, in fact, the actual findings didn't quite fit those buckets, so to clarify that, I think what I would like to do is ask Dr. Brian Kearney to come up and show you the data, so that you can understand why we moved into a little bit different range of creatinine clearance for our dose recommendations.

While he is coming up, remind me again. The second question, you wanted to know about people who had dose reduced and was there a change in response, and we will come back to that.

DR. KEARNEY: Brian Kearney, Gilead Sciences.

As Dr. Brosgart mentioned, we conducted a single-dose pharmacokinetic study in non-HBV infected patients with varying degrees of renal impairment. They were stratified by renal impairment based on this nomogram right here, consistent with FDA and ICH guidance.

In this study, we determined serum pharmacokinetics and then also renal pharmacokinetic parameters. In the study, we identified that the renal clearance of adefovir is

proportional to calculated creatinine clearance, as the adefovir is eliminated as unchanged drug in the urine.

[Slide.]

As you can see by this figure here, there is a linear correlation between calculated creatinine clearance on the X axis and the renal clearance of adefovir.

At reduced renal functions, we did see increased serum exposures of adefovir.

[Slide.]

This slide shows AUC on the Y axis as a function of creatinine clearance. We did not see substantial increases in adefovir systemic exposure or AUC specifically until a creatinine clearance was less than 50 mL/minute.

We then used pharmacokinetic modeling to simulate what steady state adefovir exposures would be in patients greater than 50 mL/minute and in patients with either moderate or severe renal impairment.

[Slide.]

As you can see, patients with either severe renal impairment or moderate or severe renal impairment have accumulation of adefovir.

Through this pharmacokinetic modeling--and this is a modeling that was actually used to select our dose interval guidelines--we identified these dose interval adjustments to use the currently available 10 mg dose to prevent unnecessary adefovir accumulation and also targeting low trough concentrations in these impaired populations that are similar to those observed in unimpaired patients receiving the 10 mg.

We are planning on studying these dose interval guidelines in the upcoming pharmacokinetic and safety study.

DR. BROSGART: It looks like my colleagues are having trouble finding those slides. I can't speak to the numbers of patients who were dose reduced. One percent of placebo patients, in Study 437, had a dose reduction. This was done in a blinded fashion prior to week 48. Three percent of the adefovir 10 mg patients had a dose reduction, and 21 percent of the 30 mg patients had a dose reduction.

The dose reductions in 30 mg were for changes in serum creatinine at the 0.3 to 0.4 level. A couple of the reductions in the 10 mg were for that. There were a few patients who had a

dose reduction when a physician saw a change in ALT, and these were an unauthorized dose reduction. Then, for the 1 percent in the placebo patients, those were also for changes in serum creatinine of 0.3 to 0.4.

When we changed our dose reduction strategy and eliminated it, many patients, actually, the majority of patients in Study 437 were coming towards the end of their first year, so the patients who had dose reductions were very few in placebo or 10 mg, and fairly substantial in the adefovir 30 mg, which contributes to our assessment that 30 mg is not favorable for long-term dosing.

The efficacy results that we see, the primary efficacy results are the week 48 biopsies, and the dose reduction strategy did not seem to impact those changes. Remembering, for those of you who reviewed adefovir for HIV, that the changes in renal function generally were not observed until after 20 to 24 weeks of dosing, so that patients would have had substantial treatment and a chance to receive benefit.

So, we did not see a correlation in the 10 mg dose, our target registration dose, where there were so few dose reductions. In Study 438, only

one patient was managed with a dose reduction, and then we amended the protocol, so dose reduction wouldn't have affected efficacy there.

DR. WOOD: I have got another question regarding resistance. You presented resistance data out to week 48. It is very interesting that the FDA data goes out on to week 96, in which there is a significant return of the entire cohort for both studies in terms of increasing HBV DNA.

I am curious, have you all performed any resistance studies from patients who have made it out to 96 weeks?

DR. BROSGART: When the agency presented their data in the second 48-week period, they did not censor for the data the first misallocation, so one really can't make heads nor tails of the ALT data or the HBV DNA when done in that fashion.

What one has to do is actually censor the data and then you can see in the as-randomized groups what is the benefit on adefovir 10 mg continuing as compared to discontinuing adefovir, as compared to initiating adefovir.

What you see when you look at the actual plots for patients, at the end of 437 or 438, if a patient discontinues treatment and goes to placebo,

there is a return towards baseline, and you can begin to see that happening within 4 to 8 weeks after discontinuing.

For patients who continue on adefovir, there is continued benefit, and I can show you that here.

[Slide.]

So, if we look in either the e-antigen-positive study 437 or the e-antigen-negative study, and now censoring data, because at the misallocation of dose, if a patient was supposed to be on adefovir 10 mg, and they accidentally got placebo, well, then, they are not on a antiviral, so having censored this now, you see the 3 1/2 to 4 log reduction out to week 48, and then beyond week 48, this is sustained, and at week 72, we see another point, 0.3 log reduction in both groups.

If you look a bit farther out, although the numbers are smaller there as the impact of the misallocation is in Study 437, after week 72, so we truncated it at week 72. In patients who continue on, though, you get about another half-log reduction, and we have seen that in our other studies where patients have been dosed longer.

We certainly are conducting resistant surveillance during the second 48-week period to look prospectively at whether or not patients have viral rebound, whether or not there is any evidence of change between the week 48 and the week 96 genotyping, and that work is all still ongoing. The studies are still ongoing studies.

When that data becomes available from the Year 2 analysis, we will certainly be sharing that with the agency.

DR. GULICK: Dr. Sherman.

DR. NGUYEN: Mr. Chairman, could I just clarify a couple of points?

DR. GULICK: Okay.

DR. NGUYEN: Actually, with respect to the last question, the resistance database that we have reviewed, it actually only went up to week 48. The information that we presented with respect to serum DNA in 437 and 438, we plotted all the serum DNA all the way down to as far as we could. So, the resistance database only went up to week 48.

Another point that I think the previous question was whether somebody looked at the DNA in patients who had dose reduction, and, in fact, we did for those patients in 435 who went from 10 mg

to 5 mg.

We looked at the DNA pattern on these people and we did not detect any loss in virologic suppression.

DR. GULICK: Thanks for those clarifications.

Dr. Sherman.

DR. SHERMAN: Thank you. A few questions.

Acknowledging the significant improvement with adefovir versus placebo in antiviral efficacy, I am curious about the greater than 1 log drop seen in the combination of the two studies in the placebo arm.

I believe this is greater than the half-log range of variability that is inherent in the assay that was used to survey the HBV DNA levels. I wonder if there is an explanation for this or if you have considered the possibility that there was contamination in the placebo arm with active drug.

DR. BROSGART: The log reduction seen in 437 is a 0.55 log reduction at week 48, and when you look at what is driving that log reduction, and if you remove the patients who are natural seroconverters in the placebo group from that, you

understand that they are largely what is driving that.

If I could get that slide brought up.

[Slide.]

This looks at median change in serum HBV DNA by e-antigen serostatus at week 48, so on the lefthand side, these are patients who have e-antigen loss, whether it is e-antigen loss alone or e-antigen loss and e-antigen seroconversion, and you will see that the adefovir 10 mg patients with either e-loss or e-seroconversion have a 5 log reduction at week 48.

There are 17 placebo patients of the 171 treated who naturally have undergone either e-antigen seroconversion or e-loss, and this is a rate that is consistent with what has been described in the literature or in the other development studies for treatments for hepatitis B.

With a natural e-loss or natural e-seroconversion, they have a 2.8 log drop. If we then look at the rest of the patients, 125 placebo patients, you see a 0.4 change in serum HBV DNA over the course of the 48 weeks, and for the adefovir 10 mg patients, a 2.8 log drop.

So, there is always a treatment difference

and a significant treatment difference between adefovir-treated patients and placebo. The placebo change in HBV DNA is consistent with the natural history of disease.

When we include patients in clinical trials, we are selecting out a group of patients who have active disease, and by "active disease," they have to have above a measurable threshold of viral replication and above a certain level of ALT, so these are patients whose disease is more active, they are more immunologically active, and we would expect, then, for there to be some decline from that over time.

This was seen also in lamivudine studies. Now, the second part of your question was what about the larger log drop that is seen in the e-antigen-negative patients, and in the e-antigen-negative patients, they don't undergo e-seroconversion.

[Slide.]

But there is a very chaotic nature to e-antigen disease. This comes from the Hadzyannis paper in Hepatology of October 2001, and there were a number of case studies in that article to demonstrate the variable course of

e-antigen-negative disease.

The ALTs are shown in white. You can see these tremendous outbursts of ALT activity. These are not patients who are being treated, so ALT is going way up, dramatically coming down over a six-month period, kind of quiescent for six months, again a peak, down up, down up, down up. I hate roller coaster rides, and I get a little nauseous just looking at this.

But if you look at the HBV DNA, you can see here this patient is kind of rather quiescent, a huge burst in HBV DNA, then, a tremendous decline, quiescent again, and then along with the increase in ALT, you see a burst again of viral replication.

So, what you are seeing in the placebo group for the e-antigen-negative study is completely consistent with what has been described in the literature for the course of patients. We have individual plots for each of the patients in our study and they look very much like this.

So, the HBV DNA change at week 48 and over time, we had patients who were coming in to study, they had to come in to study up here, so the fact that they go down over the course of a year, of

course, a different amount for each patient seems to make sense.

DR. SHERMAN: That seems a reasonable explanation. Is that consistent with Dr. Nguyen's analysis where he showed the 0.99 and 1.23 log drop that you did not censor for the e-antigen conversions?

DR. NGUYEN: In our analysis that we presented here, we did not censor for the e-antigen conversion, because we know that these people actually got about a 0.3 log suppression on average.

We would like to echo Carol's comment about the fact. We had a long discussion over this issue also, and perhaps the explanation is these people were identified for enrollment because they came in with some signs and symptoms, so probably at the time they experienced certain kind of flare, so they were easily identifiable for enrollment, and hence, with time, you can see in the placebo group the flare starts to go away, and then the ALT actually significantly drop in these people also.

So, that was sort of a plausible explanation that we came up with. Other than that, we also scratch our heads over these two

observations.

DR. BROSGART: Maybe I can just make one more comment, Ken. We did baseline genotyping and then we did the genotyping again at week 48. If there was surreptitious drug taking by patients, and particularly if they were taking it over the course of a year, if patients were taking lamivudine because they somehow suspected, oh, I got placebo, I will take lamivudine, given what the rate of lamivudine resistance is with one year of therapy, we would have seen the emergence of the prototypic lamivudine resistance mutations, the YMDD mutations at week 48, and we did not demonstrate any mutations within the YMDD motif in either study at week 48.

DR. SHERMAN: The second question is for Dr. Nguyen actually. You mentioned the two cases of nephrotoxicity that you noted and were concerned that this was attributable to the adefovir.

You also noted these patients were post-transplant, on cyclosporine, and I wonder if your analysis went into enough depth to identify patients who had potential rejection events and had increased doses of cyclosporine or other agents that are also nephrotoxic.

DR. NGUYEN: Yes, we did take all of those confounding factors into consideration when we went to do the case-by-case analysis. For example, let me just go back to Case 1. The patient actually was on cyclosporine, which we know it is a nephrotoxic drug, and the patient had liver transplant back a few years back.

The creatinine, if you look at the creatinine level, you can see that at baseline, it was about 1.5 and about eight months in, the level was still about 1.5, and then it started to slowly, gradually going up, so we do have the lead-in period of time that we don't think that the other nephrotoxic drugs were actually causing the increase in the creatinine, and the temporal relationship, there is a lag phase and then they start, the serum creatinine starts to go up. It is pretty much consistent with the historical data that we observe in the HIV program.

So, we think that for those cases, we do believe that there are suddenly other contributory factors would have to be completely ruled out, but we just could not completely rule out the contributory factor of adefovir in these cases.

We did take into consideration these

confounding factors. Certainly that is one of the issues that we would like you to comment on is the strength of association between the treatment emergent nephrotoxicity versus the drug, and that is one of the issues that we would like you to comment on later.

DR. BROSGART: Ken, if I could just comment on that. We also agree that in some of those cases, patients did have increased exposures to adefovir, and adefovir certainly could have been contributory, and agree with Dr. Nguyen that it is very difficult, there are so many other things going on, but if they did have increased adefovir's exposures, adefovir could have contributed to that.

We did have those cases reviewed by nephrologists, and actually Paul Klotman is here, and if you would like to hear his assessments of those cases, I would be happy to have him come up and speak to those same cases.

DR. SHERMAN: I don't think that is necessary now unless other members of the committee--

DR. GULICK: Let's go ahead.

DR. SHERMAN: The last question is just a clarification. Can you comment on interactions

between adefovir and other nucleoside analogs that require phosphorylation, is there any direct interaction for phosphorylation or metabolism with d4T, AZT?

DR. BROSGART: So, you are looking at intracellular, not at drug interactions here.

Dr. Xiong from our Virology Department is going to speak to that.

DR. XIONG: Shelly Xiong from Gilead Sciences.

[Slide.]

We performed our in vitro drug combination studies between adefovir with lamivudine, tenofovir, and two other nucleoside analogs in development for HBV. Our in vitro study shows in cell culture the combination of adefovir with lamivudine or adefovir with tenofovir showed only additive anti-HBV activity, and there is no synergistic cytotoxicity observed for the combination of those drugs in vitro.

DR. SHERMAN: So, you don't require phosphorylation of your prodrug.

DR. XIONG: Adefovir requires two steps of phosphorylation and tenofovir requires two additional phosphorylations. Lamivudine, as a

nucleoside analog, requires three steps of phosphorylation.

So, this data indicates that adefovir does not interfere with the phosphorylation of lamivudine or tenofovir when tested in vitro.

DR. SHERMAN: And you did not do d4T or zidovudine?

DR. XIONG: Dr. Carol Brosgart maybe can comment on that d4T drug-drug interaction.

Yes, drug combination of adefovir with d4T has been studied in vitro in our previous HIV program, and additive or synergistic anti-HIV activity has been observed in vitro.

DR. SHERMAN: Thank you.

DR. GULICK: Dr. Fletcher had a follow-up question to this question.

DR. FLETCHER: As a follow-up to this question about in vitro or intracellular phosphorylation, what about the Shutes [ph] paper in Nature and Medicine that showed adefovir appeared to be able to upregulate MRP4 and cause an eflux of zidovudine monophosphate from the cell? Of course, if that would happen, then, you would presume that that would decrease the active triphosphate concentration, so relevant to Dr.

Sherman's comment.

Do you have a comment on that?

DR. BROSGART: I will have in just a minute. Norbert.

DR. BISCHOFBERGER: Norbert Bischofberger, Gilead Sciences.

It is true that MRP4 gets upregulated, and that is a transporter for nucleotides out of cells, however, the selection of that cell line was done at 100 micromolar of adefovir, cytotoxic concentration, whereas, I want to remind you that the Cmax concentrations that occur in dose are about 28 nanomolar, so this is about 10,000-fold higher concentrations than is achieved in the clinic, and we do not believe that that mechanism of MRP4 upregulation should be observed with the current hepatitis dose.

DR. GULICK: Just to remind people, in the interest of time, we have a lot of people who haven't had a chance to ask questions yet, if we could keep the questions maybe limited to two each and the responses concise and to the point, I would appreciate it at least.

Dr. Hollinger, you had a follow-up question to that?

DR. HOLLINGER: That same question on the phosphorylation. Ribovirin also is phosphorylated and it enters red cells, which do not have a dephosphorylation mechanism. I presume adefovir also gets in the red cells, as well.

Is there any particular problems related to those two compounds or to even adefovir in the red cells?

DR. BROSGART: Dr. Hollinger, I didn't hear the last part. I heard the ribovirin, but not the rest.

DR. HOLLINGER: Whether there is any problems with either adefovir in the red cells, which I would presume also accumulates in the red cells, or its effect with ribovirin.

DR. BROSGART: There has not been a problem with ribovirin, and to speak to that, Dr. Bischofberger.

DR. BISCHOFBERGER: We have looked at the intracellular phosphorylation of adefovir in the presence of ribovirin, and the result is that it does not influence the phosphorylation or the intracellular metabolism.

With regard to RBCs, adefovir does get into RBCs very well. We have looked at that in

monkeys, however, in multiple-dose studies, it does not accumulate.

DR. GULICK: Dr. So waiting patiently, and then Dr. Stanley.

DR. SO: I just have two questions. One is on your Study 438, how many percent of those patients are hepatitis B e-antibody positive?

DR. BROSGART: How many were e-antibody positive? They all were.

DR. SO: They all were.

DR. BROSGART: Yes, 100 percent.

DR. SO: And the other question, to follow up what Dr. Wong was trying to get at, do you base your decision to deal with the nephrotoxicity problem in prolonging the interval of dosing rather than reducing the dosing? Is that based on pharmacokinetics?

DR. BROSGART: Dr. So, if clearance of a drug is affected by change in renal function, then you have two different choices. If you want to not increase exposure, you can either change interval or you can change dose.

At this time in the program, we have the 10 mg dose moving forward commercially. We also have a liquid formulation that is in development

and will be ready later this fall. So, as we move out into the commercial world, provided the drug is approved, we would have the 10 mg dose, and given that that is what we have, then, if patients need to use adefovir, then, we need to alter interval to approximate the trough concentrations that one would see, or the AUC that one would see with 10 mg in a patient with normal renal function.

Once we have our liquid formulation available later this fall, which we will be using in our pediatric development program, it then will allow us to look at the pharmacokinetics of changing dose in renal impairment.

Through our study, Study 526, that we are conducting in patients with renal impairment and chronic hepatitis B, we will be able to assess what is the best management strategy in patients, is it dose interval change or is it dose change. But when we are initially licensed, we would be doing a dose interval change because that is what we have available at this time.

DR. SO: As someone who has looked after a lot of the transplantations right after transplant, and dealing with all these potentially nephrotoxic drugs, you know, a lot of these drugs, we actually

ended up having to measure levels to guide us.

Have you actually thought of, do you think there is a need to measure levels in this very complex population where almost all of them suffer from some degree of renal impairment right after transplant?

DR. BROSGART: We have discussed whether or not therapeutic drug monitoring would be appropriate in that setting, but we also want to look very carefully at these dosing strategies in chronically infected patients over the long term.

If we are able to determine from our safety and efficacy study, which is a very careful pharmacokinetic study, that the dose interval adjustments are appropriate in a broad range of patients with varying degrees of renal impairment, then, therapeutic drug monitoring wouldn't be necessary as a way to manage patients, but we do have an assay available for measurement of adefovir levels.

It is not widely available commercially, it is a research tool at this point, but it is certainly something that could be considered in the future.

DR. GULICK: Dr. Stanley and then Dr.

Hollinger.

DR. STANLEY: I was actually intrigued by the slide that you showed on the seroconverters, the Hbe. Can you put that slide back up again and let me ask you a couple of questions?

DR. BROSGART: Is this the one where we were looking at the difference in viral load?

DR. STANLEY: No, the one that showed the 11, the longer follow-up, that 11 of them seroconverted.

DR. BROSGART: Sure, the durability of seroconversion.

DR. STANLEY: Right.

DR. BROSGART: While they are pulling that up, do you want to just go on with your question?

DR. STANLEY: One question was obviously, on the second group of them, there were nine that had gone from the adefovir to placebo, and you are following them for 72 weeks, and they have all maintained their seroconversion. How are they doing clinically, what kind of viral loads, are they off treatment completely?

DR. BROSGART: This is from the pivotal study database, so this comes from patients still in blinded therapy. It was a two-year study. Now,

patients in 437 have all completed, and they are in varying types of follow-up, either they are in their open-label phase, or they have gone to a long-term safety and efficacy study, or they have gone to the durability of seroconversion study.

So, this data that we have right now was the data in the database, and it reflects patients having a full 48 weeks in Year 1, then, their 48 weeks of follow-up in Year 2, and then additional follow-up either in off-treatment follow-up, or in open-label phase, or in moving over to the durability of seroconversion studies, so we were capturing all types of follow-up.

But, yes, they are remaining seroconverted, they are remaining with durable responses in terms of their other efficacy parameters.

DR. STANLEY: So, are most of the patients that you have had in these studies, now on some sort of adefovir treatment regimen after the 96 weeks?

DR. BROSGART: We have different options for patients. It is kind of like going to a restaurant, there is a menu. If you were a 10 mg patient in Year 1 or Study 437, then, you go if you

are interested in continued follow-up, to the long-term safety and efficacy study.

If you were a 10 mg patient from either Year 1 or Year 2 of Study 438, because Study 438 didn't have the problem during its second year of study, so all the patients who received 10 mg during any time period in either Year 1 or Year 2 in the e-antigen-negative study, they are all being offered enrollment in the long-term safety and efficacy study.

The seroconverters from the e-antigen-positive study go to Study 481, which is our durability of seroconversion study, and then for patients who were either on 30 mg in Year 1, or who haven't seroconverted, or who were in the placebo arm of Year 1 in the Study 437, have gone to yet again another study, Study 480, which is the continued access study, which allows patients in these different 18 countries to get adefovir until it is commercially available to them.

So, everybody has an option.

DR. STANLEY: Then, I just had a question. I am sorry I had to step out and if you have already answered this, I can talk to one of the panel members.

Dr. Nguyen, did you answer any questions about the 460i data that you showed on HIV coinfected resistance?

DR. NGUYEN: Not yet.

DR. STANLEY: Let me go to that then. The question I had, it was not clear to me, and this is fairly simple I think. On the first slide where you had it as a second bullet at the bottom.

DR. NGUYEN: Which slide number is that?

DR. STANLEY: Slide No. 41. Are these data from baseline enrollment or are they during treatment where you are talking about the R462G mutation?

DR. NGUYEN: I think that question probably is more appropriately addressed by our virology team members, so let me just ask one of them to respond to you.

DR. GULICK: Is it possible to get the slide up, too, No. 41 of the FDA presentation?

DR. MISHRA: I am Lalji Mishra, FDA.

The mutations R462G, they were seen at week 48.

DR. STANLEY: Okay. So, those are from week 48, those results.

DR. MISHRA: Yes, 7 of the 20.

DR. STANLEY: And then on the next Slide 42, is that also true? You say 13 patients with available HIV RT genotype data.

DR. MISHRA: Yes, that is for K65R and K70E is for week 48. Then, the M184 mutations were persistent at baseline week 48 and beyond.

DR. STANLEY: Thank you.

DR. BROSGART: Dr. Stanley, if I can just add a little bit to that study. These are HIV patients who have had long-term exposure to any retroviral agents, who developed lamivudine resistance after on average about 20 to 24 months of being on lamivudine.

They then had continued exposure to lamivudine for approximately another 21 months before entering the HIV coinfection study. To come into the study, which was an open-label study in a cohort of 35 patients, their HIV RNA had to be controlled.

It was their HBV DNA that was uncontrolled, because they were going to be treated for the lamivudine-resistant HBV, and the 35 patients then who entered, at screening, had an HIV RNA less than 400.

Between screening and baseline, it was a

little bit different and 13 of the patients that came into study actually had an HIV RNA above 400. They had enough HIV RNA that could be amplified by PCR, so you were able to get baseline genotypes, not in all 35 of the patients, but just in the ones who had enough HIV RNA to measure.

Then, at week 48, we were able then to do paired samples on patients who had measurable HIV RNA. When I say "we," it was actually the investigators in France, Drs. Thibault and Calvez and Benhamou. So, that is where that data came from.

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

DR. HOLLINGER: I have one follow-up and two questions.

On your Slide 43, I think it was initially, you presented some data--this goes back to this flare--presented some data of patients who were treated with adefovir for 48 weeks and then they continued to receive adefovir. There were 6 percent of them that had a flare greater than 10 times the upper limit of normal.

Were those patients looked at for resistance, and what happened to their HBV DNA

levels during that flare?

DR. BROSGART: These are patients who are in the second year of the study, so the 96-week resistance evaluation or genotyping is not yet complete. They did, to my knowledge, did not have evidence of loss of HBV DNA suppression. This is censored data. It was censored at the misallocated dose. So, it does not reflect any change that could have occurred during the second year after the misallocation of dosing.

This is similar. If I could go back to Slide 42, this was similar to the incidence that we saw during the first year of dosing.

[Slide.]

In the first year of dosing on adefovir 10 mg, we saw an incidence of 6 percent in patients having an ALT greater than 10 times the upper limits of normal.

[Slide.]

Then, going back now to 43, it is 25 percent in the patients who discontinued, but still 6 percent in the patients who continued on therapy.

DR. HOLLINGER: I think those would be a good group to look at very carefully.

DR. BROSGART: Right.

DR. HOLLINGER: It's a longer period of time that they have been treated, and it becomes probably more important.

DR. BROSGART: I don't need to go back to the slide, but I did show the efficacy data beyond 48 weeks, and we see continuing e-loss and e-seroconversion, so that in the second year of the study, patients who continued to be treated with adefovir 10 mg, who were e-antigen-positive, begin to get more of an immunologic control or immunologic response to their disease, so these ALT changes, as those changes in their immunologic status occur, are not unexpected.

But we are looking, in the question about resistance, if you are wondering will we be looking at them, we are going to sequence everyone at week 96. We are also sequencing patients if they have a greater than 1 log increase from their on-treatment nadir, so whether we get them just as part of the global surveillance program at week 96, or if they have a loss of HBV DNA suppression even transiently, we genotype them.

So, we will be able to see if there is any resistance emerging.

DR. HOLLINGER: And you said, of these 10

patients, the HBV DNA levels?

DR. BROSGART: I will get back to you this afternoon with that. I am not sure I have that in a back-up slide.

DR. HOLLINGER: Okay. The next question has to do with the hemodialysis dose. I think I saw in the guidelines, you were saying that patients who were on hemodialysis would receive 10 mg every 7 days, is that correct?

DR. BROSGART: Right, after dialysis.

DR. HOLLINGER: I guess the question is, since patients are dialyzed at least 3 times a week, sometimes more depending on the place that they are at, and since the dialysis removes adefovir from the systemic blood, then, I would like to know how that equates with their therapy.

DR. BROSGART: Right, it is removed, but it is not completely removed, and I will have Dr. Kearney show you the data from that cohort in the pharmacokinetic study. He didn't show that the first time he was up. He was just showing patients with diminished creatinine clearance.

You will see from the data he is about to show, how we calculated the interval.

DR. KEARNEY: In our single-dose

pharmacokinetic study, we did observe the pharmacokinetics and studied the pharmacokinetics in hemodialysis patients during their dialysis period, and then also in between hemodialysis period to assess the clearance of drug by the dialyzer.

Hemodialysis, it was a 4-hour hemodialysis session efficiently removed adefovir, had an extraction ratio of approximately 63 percent. We were able to calculate the hemodialysis elimination rate constant, and from that, determined that a 4-hour hemodialysis session would remove approximately 36 percent of a dose of adefovir.

So, extrapolating that elimination rate constant to the total number of hours in dialysis per week, shows that once weekly dialysis would remove approximately 75 percent of a dose of adefovir.

DR. HOLLINGER: So, someone who is going to use a guideline for the use of adefovir, would one make a statement about when it should be taken? For example, if they get it Monday, Wednesday, Friday, they should have it after their dialysis on Friday, or should there be something in the guidelines about that?

DR. KEARNEY: The current dosing recommendation is to be dosed after completion of a hemodialysis session.

DR. HOLLINGER: After what?

DR. KEARNEY: After completion of a hemodialysis session.

DR. HOLLINGER: But there are usually 3 a week, and you are saying 10 mg every 7 days.

DR. KEARNEY: Ten mg once weekly after the last hemodialysis session for that week, and we are currently discussing perhaps more detailed information because especially acute, the ill patients who may be dialyzed more frequently, you may want to know total hours of dialysis that they are getting per week.

DR. HOLLINGER: It wasn't clear to me at least in that regard.

The final question, just a question maybe about the baseline biopsies. There were 63 individuals who--first of all, you biopsied a large number of them, I think that is really excellent--but there were 63 individuals who did not get a second biopsy.

I would like to know if there are any differences in the baseline biopsy of those 63

individuals versus the ones who did have a paired biopsy done at the end of therapy.

DR. BROSGART: I don't believe I prepared a slide to answer that question directly, Dr. Hollinger, so we will have to come back to you this afternoon on that. I will see what I can do over the lunch break.

DR. GULICK: Okay. Dr. Fletcher, then Dr. Kopp.

AUDIENCE: Lunchtime.

DR. GULICK: Yes, thanks for reminding us about that. I think what I would like to do is to continue questions for half an hour and then we will take lunch at 1 o'clock. We will shorten the lunch period to 45 minutes from an hour, and then proceed there.

If you are hungry, maybe you could go get a sandwich in the meantime. A lot of people, in fairness, have not had the chance to ask questions yet. Again, let me remind everybody let's keep the questions to two per person and the answers very short and to the point, and that would be helpful. Thanks again for the reminder.

DR. FLETCHER: This is probably a joint question to the sponsor and the agency. I am not

clear how to think about both the safety assessments and the response assessments after 48 weeks.

What I am wondering is does the fact that patients were able to move from drug to placebo, or from placebo to drug, perhaps, you know, downwardly bias assessments of proportion of patients that may have increase in serum creatinine, for example, and upwardly bias assessments of patients that were responding, if that makes sense?

DR. BROSGART: I am not sure I understood the question, Dr. Fletcher, so I will let Dr. Nguyen go first. We will see where he goes.

DR. FLETCHER: Do you want me to try it again?

DR. NGUYEN: You may have to because I think that is a really complicated question. Yes, please.

DR. FLETCHER: After 48 weeks, some patients on drug could move to placebo, and some patients on placebo could move to drug. So, when you look at assessments, for example, at week 96, are the rates of toxicity perhaps downwardly biased because you had patients that moved from drug to placebo, and we know if they are drug-associated in

a placebo period, they will go away, and are assessments of patients responding, are they upwardly biased because you had an increased number of patients now that went from placebo to drug?

DR. BROSGART: I think I can actually answer that question. We do censor the data, and we also look at patients in their groups as assigned in each year, but we have also looked at the all-adefovir, so any patient who received at least one dose or more of adefovir, we have looked at those patients, and there is 492 patients between the two studies who received at least one dose of adefovir or more.

Then, we censor it at the time of the last assigned dose, but you certainly can see then, in a Kaplan-Meier analysis, where you can take into account all of that varying degree of follow-up, you can get a good assessment and an accurate assessment of what the Kaplan-Meier estimates would be for toxicity, because you do have people with different amounts of follow-up, and you also can do the same with efficacy.

We can show you both, but I think we have looked at the data, I don't think it underestimates the safety or the efficacy. I think it gives you a

good assessment, because there are different amounts of follow-up.

DR. FLETCHER: My second and last question.

DR. GULICK: Thank you.

DR. BHORE: May I take a shot at answering your question?

DR. GULICK: Sure.

DR. BHORE: Maybe I don't have an answer, but one way to look at the serum creatinine in patients who switched from 10 mg to placebo would be to censor that data at the time point that they switch to placebo, and then use the available data on 10 mg to get estimates of serum creatinine.

Regarding the second group who switched from placebo to the drug, it is as if these patients delayed for 48 weeks and then started on the 10 mg dose, so one could reset their time point to zero when they started the 10 mg, and then use that data forward from the 48 to 96 and consider that as time point zero to 48, and use that to estimate the serum creatinine.

DR. BROSGART: Actually, Dr. Fletcher, that is exactly what we did. That is what I was saying, that is the all-adefovir analysis where you

look only at people who get exposed, and you count all of their exposure, so even if they started in the second year.

We did the same analysis as the agency, and we have come with the same numbers of patients who have had changes, whether it is at the 0.3 level or the 0.5 level.

DR. FLETCHER: The second question is to gender differences. In the sponsor's presentation, this would be like your Slide 21, I was just interested in the fact that the females that received placebo seemed to do better than males that received placebo, and is that consistent with the natural history, and that perhaps the women didn't quite do as well on adefovir.

So, the question is has there been analyses looking at gender differences in terms of response, and then in terms of toxicity, as well, particularly any nephrotoxicity.

DR. BROSGART: I can answer both of those. The first, I believe this was the slide you were referring to.

DR. FLETCHER: Right.

[Slide.]

DR. BROSGART: This is the integrated

summary of efficacy, which pools patients from the e-antigen-positive and the e-antigen-negative study, and looks at histological improvement either by demographic characteristics or by hepatitis B disease characteristics.

One of the first things to notice is that there are more men in the study than women, approximately 80 percent were men, about 20 percent women, so we have a much smaller cohort now. You know, you take the big group and you start dividing it up into little pieces, and as you do subset analyses, as they get smaller, you start losing some of the power you had when you had your big study.

In the female group, we have 59 women in placebo, and we have 60 in adefovir 10 mg. If you look at the histological improvement for the adefovir 10 mg women, it is 52 percent, so that is comparable and within the range for the study as a whole, compared to 37 percent response in the placebo.

So, the efficacy in the women is appropriate. What you are seeing is a little bit higher response in the placebo patients. I think this is most likely the result of the smaller

numbers of patients in these groups.

This has been an unadjusted analysis. We haven't done a multivariate analysis to control for other factors, such as, you know, what was the ALT level in the placebo women compared to the ALT levels in the adefovir-treated patients, and those are further analyses that will be ongoing.

In terms of response to safety, we haven't seen a difference in the safety profile between men and women looking at all safety parameters.

DR. NGUYEN: May I just add in a couple of comments on those issues? With respect to nephrotoxicity, especially in Study 435, because we got quite a number of people with nephrotoxicity in that study, we did not see any evidence that men or women would be more susceptible to develop nephrotoxicity. I think the ratio was just about the same as the ratio of people enrolled in the study for each cohort.

With respect to the issue of efficacy and liver biopsy, the liver biopsy that we use as a primary endpoint, that is, the necroinflammatory score, a change of greater than or equal to 2 points with no concurrent change in fibrosis, essentially, we are looking at only the

necroinflammatory activity in the liver.

So, what we did was particularly for Study 438, we looked at the changes in fibrosis similar to what we did before, for women and compared to men. We saw that the proportion of women with improvement in fibrosis is going almost the same direction as the total patient population.

In fact, the proportion of people who had improvement of fibrosis in the adefovir 10 mg group was approximately 34 percent, and 4 percent got worsening fibrosis, and for women in that study, 28 percent were actually improved compared to 11 percent getting worse.

Now, if you look at the women in the placebo, 80 percent of them remained the same, 10 percent got worse, 10 percent got better, so there was a shift. We haven't calculated whether it is statistically significant yet, but certainly the numbers point to the same direction.

DR. GULICK: Dr. Kopp and then Dr. DeGruttola.

DR. KOPP: I would like to ask three questions, if I can, but I will keep them short.

The first has to do with the issue in renal failure, do you adjust the dose or the

duration? From either preclinical or clinical studies, do you know if nephrotoxicity better correlates with peak levels, AUC, or trough?

DR. BISCHOFBERGER: In the spirit of keeping the answer short, we don't have any data from our studies to correlate pharmacokinetic parameters with nephrotoxicity.

DR. KOPP: Just a follow-up comment, I do remember in the slide that you showed of your lowest GFR group, it was on a log scale and there was a quite a bit higher peak issue as you would expect with the 10 mg dose, so I just throw that out.

The second issue has to do with I think it's the 560 study that you are enrolling patients in now to study renal insufficiency, how many patients, how long do you expect until that data comes back, and how will that come back to the FDA?

DR. BROSGART: All of our studies are filed to our IND, so first, the protocol would go to the agency for their review and concurrence. We are just finalizing that protocol now, so the agency, I do not believe has seen it yet although we have talked about it a little bit on conference calls, I don't believe they have actually seen it.

Once we finalize the protocol, we have all of the investigative sites set up, and we will be beginning shortly. We have been a little busy this summer with this activity.

[Slide.]

This is the study design. Group 1 are patients whose creatinine clearance is greater or equal to 50, but less than 80. Group 2 is in the 20 to less than 50 range. Group 3 in the 10 to less than 20, and then Group 4 in the less than 10 split into two cohorts, one, patients are non-hemodialysis patients, and the other being patient who are on hemodialysis.

These are patients who will have intensive PK, they will have chronic PK, they will also have general safety and efficacy parameters evaluated over the course of 48 weeks. The numbers of patients for each group are currently set at 12.

This is more than we had in our PK study, there were 8 patients in each cohort, but because we are going to be following patients longer, we wanted to increase the numbers of patients.

It is also likely we will have patients with lamivudine-resistant HBV because we have so much demand for that already in these patient

populations which do have diminished creatinine clearance that we know that it will be easy to enroll there patients.

The final answer is when will that data be available, if we are able to get started in the fall, which is what we want to do, and we already have the sites selected, that is already set and done, and these particular sites have been very efficient at enrolling, taking about generally a month to two months to enroll their patients, a little over a year from the fall we would have data, but certainly from the initial period, which is the intensive PK, that data we would have very shortly thereafter initiating the study.

Then, again, this would be part of an ongoing discussion with the agency, as soon as that data from the first study became available, that would be shared with the agency.

DR. KOPP: The final question is what are your recommendations for the clinician with a patient with normal renal function about the adequacy of follow-up, and how do you follow up renal function.

DR. BROSGART: In our pivotal studies, we enrolled patients who had normal renal function,

and as these were registrational studies, they had a couple measurements before starting, and then there is baseline, and we saw them every four weeks thereafter.

If there were any abnormalities, they were brought in for an off-treatment visit to confirm the abnormality, and we did that for two years in both of those studies. The incidence of renal laboratory abnormalities, that would require study drug discontinuation, was very low.

There was only 1 out of the 492 patients treated who had a discontinuation of drug for a confirmed increase in serum creatinine greater or equal to 0.5 mg/dL, and no patient had any change in serum phosphorus below 1.5 or 2.0 mg/dL.

Based on those event rates, we went back to our Data Monitoring Committee, who monitors our studies, all of our pivotal studies and non-pivotal studies, for safety, and asked them, in evaluating the data, whether or not they would be comfortable, in the patient with normal renal function, who doesn't have a history of renal dysfunction, and is not going to change renal function because they are not adding nephrotoxic agents, so no history of renal impairment, no renal dysfunction at baseline,

based on the event rates, we felt we would be comfortable going forward with monitoring at baseline and then every three months because of the event rate.

The Data Monitoring Committee concurred with us. This was put into, then, our protocols as a protocol amendment, and in our long-term safety and efficacy studies, which have been submitted to the agency and approved by the agency, patients will be followed in those studies every three months.

So, in long-term follow-up of patients with normal renal function, we have moved away from every four weeks now to every three months. Every three months meshes with how patients are followed out in hepatology offices and clinics as part of the routine management of their chronic disease.

So, what we are recommending in the package insert is that for patients with normal renal function without a history of renal impairment, that they can be monitored routinely as part of their chronic hepatitis B management, which in most cases would be every three months.

DR. KOPP: And then two follow-ups on that, if I can. One is do you define normal renal

function as normal serum creatinine or normal creatinine clearance at baseline?

DR. BROSGART: Normal creatinine clearance, and also, particularly when you are dealing with decompensated patients, the proposed package insert is very clear that creatinine clearance, if it's calculated, must be calculated based on ideal body weight or lean body mass, because if you don't do that, as you know, with a patient with ascites are very wasted, you won't get a precise measurement or a precise calculation that correlates with what the actual creatinine clearance is. So, the package insert is quite explicit on this.

DR. KOPP: And then you said that if you measured every three months or maybe I inferred this, you would not miss any patients who changed by more than what creatinine value compared to following them every month? In other words, were there any people who would have changed 0.4 or 0.5?

DR. BROSGART: Well, that is part of the assessment that we did with our Data Monitoring Committee, and we would not have missed patients, so we were comfortable moving to the every three months, as was the Data Monitoring Committee.

DR. GULICK: Dr. DeGruttola and then Dr. Schapiro.

DR. DeGRUTTOLA: Regarding the decline in ALT for the placebo patients, that looks like classic regression to the mean, but one of the ways you can investigate that is just to divide the baseline, the placebo patients at baseline into different categories according to their ALT and look at the response.

I am just curious if you have done that.

DR. BROSGART: No, we haven't done that yet.

DR. DeGRUTTOLA: Obviously, the regression to the mean can affect other investigations like the gender investigation, as well.

My other question is regarding the patients that don't have a second biopsy. I just wanted to find out if the numbers were evenly distributed across the treatment arms.

DR. BROSGART: Yes.

DR. DeGRUTTOLA: And did they seem fairly comparable in terms of risk across the two arms?

DR. BROSGART: Yes. We looked at the baseline characteristics of patients who had biopsies compared to patients who didn't, and for

demographic and disease characteristics, they were similar, and the proportion of patients who didn't get biopsies was similar in each of the treatment arms in each study.

DR. SCHAPIRO: Two quick resistance questions.

Regarding the phenotypic analysis that was done, in the briefing we received, it looked like you were looking at point mutations, but did you basically take all the patients who rebounded based on your definition and look at the change in phenotype from baseline to that point? Do you have that data?

DR. BROSGART: Yes. Let me ask Dr. Shelly Xiong who did these analyses to come up and address that issue.

DR. XIONG: For patients who showed viral load rebound and in which the substitutions, polymorphic substitutions, we did both baseline and week 48 phenotypic analysis, used the whole patient clones, including the whole 3.2 kilobases HBV genome.

The analysis for other rebound patients without substitutions is also ongoing.

DR. SCHAPIRO: Can you show us, was there

a change for those patients? Was there a phenotypic change for all the patients that you had changes for?

DR. XIONG: The change was less than 1.4-fold.

[Slide.]

As you can see, for the four patients we analyzed, the baseline IC50 range, they are all very close to each other, about roughly 0.24 micromolar. At week 48, they are also very close and the shift of IC50 for each major patient are less than 1.44.

DR. SCHAPIRO: That is just four patients. Can you show us for all the patients?

DR. XIONG: For the other patients, the analysis is still ongoing. We haven't additional data at this moment.

DR. SCHAPIRO: So, only those four right now.

DR. XIONG: Yes. We recently developed this technology because previously, HBV phenotypic analysis is limited to the engineered cytomutagenesis, but with this new technology, we are going to apply into future phenotypic analysis.

DR. SCHAPIRO: Just a quick second one.

You mentioned that for the polymorphisms and the conserved regions, you didn't find any pattern.

Could you say just statistically how that was looked at?

DR. XIONG: We analyzed the emergence of all substitutions including polymorphism in conserved site, and we didn't find specific patterns in terms of distribution between adefovir, treated arm, and placebo arm, and all individual polymorphism occurred at very low frequency, less than 1.6 percent of patients.

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

DR. SJOGREN: Dr. Brosgart, you showed an impressive improvement in histology in both e-antigen- positive and e-antibody positive patients at week 48.

My question is what indications do you have that this response is durable, that, indeed, it is going to be sustained over the course of the disease.

I am particularly worried, I will tell you why, because I heard this morning that our old friend DNA is not going to be usable, at least with this drug, because it can be up, it can be down, and it is not going to correlate that well with the

goodness of the drug.

So, I am seeing patients and treating them for 48 weeks, taking them off drug, and then what do I do then, how do I ensure that, indeed, this patient or these patients are not getting worse off.

My second brief question is are 48 weeks treatment enough with adefovir.

DR. BROSGART: First, Dr. Sjogren, I just want to clarify. The question I think that was asked this morning was essentially does the change in HBV DNA, is it a complete surrogate, does it explain all of the treatment effect, and it is not a complete surrogate, it doesn't explain all of the treatment effect. It explains part of the treatment effect.

So, measuring serum HBV DNA, I believe is still a valuable tool as part of the clinical management of patients with chronic hepatitis B.

[Slide.]

When we look at patients who have been treated in our pivotal studies, 48 weeks was the time point planned for the evaluation of the primary endpoint and some of the key secondary efficacy endpoints, but the primary endpoint, the

biopsy was performed at 48 weeks, but we have continued to treat these patients and to look at what is the additional efficacy with continued treatment beyond 48 weeks.

When you look in both populations, both the e-antigen-positive population and the e-antigen-negative population, you see continued benefit over time. There is additional reduction in HBV DNA, more patients become undetectable as measured by the Roche Amplicor assay, continuing improvement is seen in ALT reduction with more patients normalizing ALT, and when you look at the parameters in the e-antigen-positive patient, you see increasing numbers of patients just with an additional 24 weeks of therapy having had e-antigen loss or e-antigen seroconversion.

So, by every efficacy parameter, there is additional efficacy with only an additional 24 weeks of therapy.

[Slide.]

Now, I also can show you from a long-term study in HIV-coinfected patients that if you continue to provide drug beyond 48 weeks--it's 301--this was from the coinfected study that we were speaking about earlier this morning. You see

the same kind of decline in HBV DNA, a 4-log reduction at week 48. These patients tolerated their therapy, they continue their therapy.

This was the data presented at easel, and we don't have the complete 96-week data yet, we only had 13 patients at week 92, at this time point, but you see that they go from a 4-log reduction at week 48 to now greater than 5-log reduction out to week 92.

So, there is continued antiviral benefit, which you would expect if there is not the emergence of resistance, and when you look at the other clinical parameters, there is continued benefit there.

So, all of this adds together that the histology benefit we see at week 48 is added to with continued therapy in patients for whom they have not achieved any antigen seroconversion, and you can only do that in the e-antigen- positive patients, and that takes a period of time, so that most patients will need chronic therapy.

DR. SJOGREN: So, if I am to understand you correctly, only 12 percent of your patients had seroconversion, as I remember, in the previous slide. So, 88 percent of the patients will need to

go on for more than 48 weeks of treatment.

Is that a correct assumption?

DR. BROSGART: In the intent-to-treat analysis, we are missing equal failure, 12 percent of patients had seroconversion at the 48-week visit.

[Slide.]

If you look at time to e-antigen loss and e-antigen seroconversion, you actually have 14 percent by week 48, and that increases to 23 percent by week 72.

This is similar to what has been seen in other development programs. E-antigen loss and e-antigen seroconversion tends to happen slowly and the majority of patients will need therapy beyond one year.

DR. SJOGREN: That is what I was trying to get at, how many years, because sitting around this table when the agency looked at lamivudine, the data looked very impressive for 48 weeks, and then treating patients, some of them for three, four years with--obviously, lamivudine has all the problems that your drug hasn't shown at least to this point of the resistant strains.

It is quite a commitment. I am trying to

get an idea, and also in your pivotal studies, your endpoint is histological improvement, and your secondary endpoints are the ones that you have in the slide, and so I am trying to find out if you are looking at your primary endpoint at week 96 or further on to be faithful to your endpoint and tell me whether there is histological improvement particularly in the patients that have finished treatment at week 48.

DR. BROSGART: Sure. To answer the first question, adefovir, though, is different from lamivudine in that lamivudine, 24 percent of patients at one year already have evidence of resistance, and we have not seen adefovir-associated resistance in these pivotal studies in any patient treated out to 48 weeks, and in other groups of patients who have been treated out to 96 weeks, or up to 136 weeks in other studies, we haven't seen resistance mutation.

So, adefovir appears to be less prone to the development of resistance. If resistance does not develop in most patients, then, there is a very good chance that you get, not only durable, sustained responses, but that you can gain additional improvement over time.

In terms of the histology, we will be doing more look at histology. Our studies were designed to have mandatory biopsies at week 48, but to have optional biopsies at week 96.

Now, in the e-antigen-positive study where there was a misallocation of dosing in the second year, we will have very few biopsies in the e-antigen-positive study, however, in the e-antigen-negative study, that was the study that had 91 percent completion rate for paired evaluable biopsies, they are doing their biopsies, so we are going to have biopsies from week 96 to look at in patients, and I think that that will be very helpful.

Obviously, we won't have that today, but it will emerge over time, and that data will be shared with the agency.

DR. GULICK: Dr. Sun.

DR. SUN: The first question is do you have any data on the interaction of adefovir with cyclosporine.

DR. BROSGART: Thank you, Dr. Sun. Adefovir does not interact with the cytochrome p450 system, so we wouldn't anticipate an interaction, however, we are evaluating whether or not we have

an interaction because these are important concomitant medications being used by patients.

How you do that is a bit challenging. These are immunosuppressive agents, so to do a classic drug interaction study and to bring in healthy people and expose them to immunosuppressive nephrotoxic agents is not the best way to do it, so you have to be a bit more creative.

We have done some initial retrospective work trying to look back within the transplantation study at patients who had been on long-term cyclosporine dosing and who were stable in the three months prior, and then to look at were there any changes in the three months hence.

As you can imagine, it's a little bit challenging to do in a study that is being conducted in 15 countries and at over 60 sites worldwide, each of which only has enrolled a small number of patients, so that didn't seem to be the best way to go about it, so we are going to evaluate it prospectively in a new study going forward. We will be working with the agency on the best way to do that.

DR. SUN: The second question relates to the misallocation in 437. I guess the first part

of the question is do you know what was misallocated, in other words, you have this period of about nine months where drug was misallocated, and do you know what people got erroneously, or you simply don't know?

DR. BROSGART: No, we know exactly what happened.

DR. SUN: Do you know, in other words, that patient 1 got, you know, two months of 30 instead of two months of 10?

DR. BROSGART: During the second year of 437, patients only would be getting 10 mg or placebo unless, for some reason, they were on 5 mg, and there was almost no one on 5 mg from a dose reduction strategy in Year 1.

A computer system was used to allocate the bottles of study medication and each study bottle had a unique identifier. During the second 48 weeks of the study, the randomization allocation for those lots of bottles changed, and while the randomization allocation plan changed, the computer system, the new program for the computer system was not appropriately implemented by the contractor who ran that portion of the study.

As it was not reprogrammed, it meant that

study medication was dispensed according to the old treatment assignments in the lots of allocated numbers previously, and what that ended meaning is that after a median follow-up of 16 weeks in the study, beginning with September 22nd of 2000, 416 patients received at least one month or more of misallocated drug.

The misallocated drug was either adefovir or placebo, and so a patient who was on adefovir 10 mg, as planned by the study is appropriately randomized, the randomization was correct for the patient, might on an individual month, at some point after September 22nd until July 19th, when we were aware of the problem, could have received on alternating months placebo, and on the same hand, someone who was on placebo, might have gotten a month or more of adefovir.

So, the only misallocated drugs were adefovir or placebo. Once we identified the problem, we stopped the study, we immediately unblinded the study, and each physician was provided with all of the safety and efficacy data unblinded except for the--this was all after the primary analysis had been done for Year 1, and they were given what dose the patient was on for each

month, so that they were able to determine if there had been any changes in either HBV DNA or ALT, they were able to see and understand how it had occurred.

Then, as soon as the protocol amendment was implemented locally, then, the patients were able to go to open-label adefovir.

DR. SUN: So, in terms of safety now, since you know what people got, how did you classify these patients in terms of the safety after Year 1?

DR. BROSGART: Well, what we did is we censored safety and efficacy data for the primary analysis at the date of the first misallocated dose. We then evaluated, for each individual patient, we evaluated their safety profile and their efficacy profile in different phases.

So, there is week 48, which is fine. There is post-week 48 as appropriately randomized with a median follow-up for the population as a whole, of 16 weeks, but that could range from anyone having a few days up to someone else having had a full 96 weeks of correctly allocated dosing.

So, the first 48 weeks, then, they have appropriately allocated randomized second-year

dosing. Then, there is the misallocation, they are censored. Then, they have their misallocated period, and then the blinded study ends, and that ends the misallocated period.

Patients then went into an off-treatment phase, which ranged from almost no days at some study sites where they have very fast IRBs, to a little bit longer where it can be slowed, and then patients went to open label.

We have evaluated safety and efficacy in each of those phases, and that was all included in the original NDA and then updated as part of the NDA safety update.

DR. SUN: So, just the last point on that. So, in your category where you say, "All adefovir 10 mg, zero to 96 weeks, with an N of 492"--

DR. BROSGART: That is censoring patients at the first misallocated dose.

DR. SUN: Okay.

DR. GULICK: That is the end of the my list. I would like to ask one question myself before we break.

DR. BROSGART: The chairman gets a question?

DR. GULICK: Actually, a two-parter.

What is the mechanism of nephrotoxicity with this drug?

DR. BROSGART: The mechanism of nephrotoxicity has to do with uptake in the renal tubules, and to address that issue, Dr. Bischofberger is going to come up.

Every once in a while I get to have a preclinical or non-clinical question, I get a break.

DR. BISCHOFBERGER: I am going to make it short. Could I have the slide.

[Slide.]

DR. BISCHOFBERGER: So, what it is, is we have a lot of preclinical evidence now that a renal transporter is involved, so this is the tubular cell here with a lot of transport systems. One of them is human organic anion transporter 1, and that we think is the protein or the transporter that is responsible for transport of adefovir into the tubular cell.

Adefovir then concentrates in this cell and causes local cytotoxicity. We have meanwhile cloned and expressed the human organic anion transporter. We looked in different tissues, where does it occur, and as you see, of the many tissues

isolated, only the kidney expresses significant amount of this.

We have also looked at transport efficiencies, inhibitory molecules, et cetera, and I can get into that more if you are interested.

DR. GULICK: So, the direct cytotoxicity on the renal tubular cells is known?

DR. BISCHOFBERGER: Yes, we actually don't know what the actual molecular mechanism of the cytotoxicity is, but what we have done with this human organic anion transporter, we transfected it into normal cells, CHO cells, I think they were, and we found that those cells now were able to get a lot more adefovir into the cell through this transport mechanism, and the adefovir was more cytotoxic, it just killed the cells, but we actually don't know what the molecular mechanism of the actual cytotoxicity is.

DR. GULICK: It is not thought to be mitochondrial toxicity?

DR. BISCHOFBERGER: It could be. We have not looked at that per se.

DR. GULICK: Just in a related question, what percentage of people who have renal abnormalities have irreversible renal abnormalities

either from your 30 mg group or from the 735 study?

DR. BROSGART: From the 435 study--

DR. GULICK: Sorry, 435.

DR. BROSGART: --it would be very difficult to assess, and the reason being these are patients who, by and large, don't discontinue their drug. These are patients who are wait-listed for transplantation with lamivudine-resistant HBV, whose hepatitis is out of control or they are post-transplantation, and they are in danger of losing their graft.

So, these are patients who are struggling to hold on to life, and even when their renal function changes, the physicians would work with us in whatever way we were willing to work with them to adjust dose, so that patients could stay on drug.

The changes seen in renal function in those patients are complex because they were occurring in and around new surgeries, sepsis, et cetera, so that the patients continued on drug--

DR. GULICK: Can I just stop you? Let's focus, then, on the 30 mg, the patients with normal renal function who got 30 mg, what percentage had irreversible renal changes?

DR. BROSGART: Patients resolved upon discontinuing drug.

DR. GULICK: One hundred percent?

DR. BROSGART: In the patients in the 437 study, they resolved upon discontinuing drug. The patients were only dosed for 48 weeks on 30 mg. The changes occurred between generally, you know, 6 months and 12 months, and then patients came off of drug.

DR. GULICK: So, it was 100 percent reversible in anyone who had an elevation in creatinine on that study?

DR. BROSGART: In the 437 study, yes.

DR. GULICK: Okay, great.

DR. NGUYEN: Mr. Chairman could I just make a comment on that?

DR. GULICK: Okay.

DR. NGUYEN: According to our analysis for the patients in the 30 mg group, the percentage of people that resolved, that is, you know, with the serum creatinine going to below 0.2 mg/dL was 61 percent.

DR. BROSGART: But actually, though, Tan, for the patients who had a creatinine greater or equal to 0.5 mg/dL above baseline, the protocol

definition of resolution was less than or equal to 0.3, and that was the analysis I was speaking to.

DR. GULICK: So, 100 percent of people returned to less than 0.3.

DR. BROSGART: Less than or equal to 0.3 for patients who had a greater or equal to 0.5.

DR. GULICK: Okay. That seems like a good place. In the immortal words of somebody, it's lunchtime.

DR. BROSGART: I think there were two people who said that.

DR. GULICK: At least.

We will break until 2 o'clock. Thanks.

[Whereupon, at 1:15 p.m., the proceedings were recessed, to be resumed at 2:00 p.m.]

AFTERNOON PROCEEDINGS

[2:05 p.m.]

DR. GULICK: Hopefully, everyone had a good lunch.

There were a couple members of the panel who didn't get a chance to ask questions, so Dr. Brosgart, if you wouldn't mind, and the agency, too, I just wanted to give the other panel members who hadn't had a chance to ask any questions that they had.

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

DR. ENGLUND: I had two quick questions. Do you have any information with any of the other immunosuppressors besides CSA, besides cyclosporine, or are you planning to collect that?

DR. BROSGART: The data we will be collecting is with both cyclosporine and tacrolimus, and in the patients, about half of the patients were on cyclosporine, about half were on tacrolimus, and then there was a small percentage that were on both of them concomitantly.

DR. ENGLUND: I just wanted to make sure that you weren't just limiting it to cyclosporine.

DR. BROSGART: No, I think the question that was asked specifically by Dr. Sun was were you

addressing cyclosporine.

DR. ENGLUND: Then, I have another question. This goes back to your study design. Do you have, for those of us on the committee, I am a little bit confused as to the numbers of patients, who got what, in your 437 study after week 48. I understand there are reasons for it, but were there any participants that really got placebo afterwards? I don't want median, I want like more than numbers.

[Slide.]

DR. BROSGART: Well, these are the numbers of patients who continued on the 437 study, so of the 511 patients who entered at week zero, at week 48, 142 of the adefovir 30 mg patients went to placebo. Of the 10 mg patients, the 171, 71 of them went to placebo as randomized, and 85 went to adefovir.

In the placebo group, 167 patients, 138 went on.

DR. ENGLUND: We know that, right, but then accidents happened. So, did any of the people that were assigned to placebo, actually get placebo for the next 6 months?

DR. BROSGART: The misallocation of dosing

occurred after patients were already randomized and on their as appropriately randomized therapy, and during the misallocated period, patients received misallocated drug, and every month it could have been something different.

So, some patients had no misallocated drug, some patients only had one month of misallocated drug, so if they were supposed to be on placebo, they received one month of adefovir 10 mg during this misallocated period, and some patients who should have been on 10 mg received one month or more of placebo during the misallocation period.

DR. ENGLUND: Do you have a table summarizing what people actually got, what the recipients actually received, for example, of the placebo? Were there any that continued to get placebo? You have given us medians of how many weeks they actually got.

DR. BROSGART: Each of 416 patients received at least one month or more of misallocated drug, so patients who were supposed to be on placebo, got placebo as randomized until their first misallocated dose, and the data is censored for each person. Each individual's amount of

follow-up, therefore, is different in the appropriately allocated period and in the misallocated.

We have month-by-month data for each individual patient, where you can look for each individual patient to see what they got, but it is not as if there was a pattern where one month everybody only got placebo.

DR. ENGLUND: No, I was just hoping you had a summary slide that showed if patients--

DR. BROSGART: It would be difficult to summarize like that. You can summarize median time in the different phases, but then you really have to go to the individual patient to understand what happened in each patient experience.

DR. GULICK: Dr. London, I believe you had a question.

DR. LONDON: This has to do with preclinical studies, and you said that there were studies in woodchucks, and my question is were those carried out long enough to know whether liver cancer occurred at the same rate, was delayed, was reduced by the adefovir treatment?

DR. BROSGART: Right. I will have Dr. Taylor come up to discuss our preclinical studies,

or actually, does Dr. Gibbs want to answer that?

The woodchuck studies were carried out for 12 weeks.

DR. GULICK: There are several follow-up things. The sponsor asked that we give them a little more time.

DR. BROSGART: Actually, I have the answers.

DR. GULICK: Are you ready to go?

DR. BROSGART: Yes. I told you I just needed a little more time.

DR. GULICK: Well, we gave it to you, I guess.

There were a couple questions that came up in the question and answer that they wanted a chance to respond to.

DR. BROSGART: The first question, there seemed to be some confusion as to whether or not it had been answered and clarified or not, and that had to do is there a difference between people who had biopsies at week 48 and who didn't undergo biopsies at week 48, was there a difference in those patients.

There was not a difference in baseline Knodell score between patients who had biopsies and

didn't have biopsies, and it occurred equally distributed in the different treatment arms.

So, I thought I had answered that, and then someone said they thought I hadn't, so I just wanted to make sure that that question was answered.

My understanding is there were two questions that we needed follow-up. One was in the patients who continued on adefovir in the second year, the 164 patients, in the 6 percent who had ALT flares, what happened with the HBV DNA.

What appears is that there is a transient blip up in DNA at the time of flare, but all the flares resolved, and as the flares resolved, the DNA came back down. So, that was the answer to that question.

The next question--and I am not sure who asked it, whether it was Dr. Sjogren or Dr. Sherman, I know it was from that corner--had to do with worsening of histology in patients who had HBV DNA less than 400.

In Study 437, there were 10 patients with an HBV DNA less than 400, who didn't have histological improvement, and by that, I mean the primary endpoint, at least a 2-point decline in the

Knodell necroinflammatory score with no accompanying worsening in fibrosis, but when you actually look at their individual scores, 9 out of 10 of those patients had no worsening in their Knodell score, 1 out of 10 increased by 1 in necroinflammation and by 1 in fibrosis.

Of the 10, 3 had hepatitis B e-antigen seroconverters, 5 had e-antigen loss, in 1 there was no change of sero status, and in the last patient of that 10, their e-antigen status was missing at week 48.

In terms of ALT, in 9 out of the 10, their ALT had normalized, and in 1 out of 10, it was mildly elevated. This is consistent that if you are beginning to see an immunological improvement, even if the HBV DNA is suppressed, you may not see improvement in the liver biopsies because you may be seeing a response to the improved immunological control.

In Study 438, there were 21 patients less than 400 who did not meet the primary endpoint. Of those, 20 out of 21 showed no worsening in their Knodell scores, 1 out of 21 worsened. You can't look at e-antigen seroconversion in that population, but for ALT, 18 of the 21 had

normalized and 3 of the 21 were just mildly elevated above the upper limit of normal.

So, we see improvement in almost all of the patients in terms of other efficacy parameters including not having actual worsening of their Knodell scores. It is just that they didn't meet that primary endpoint of at least the 2-point decline in Knodell necroinflammatory score with no accompanying worsening in fibrosis.

So, I think those were the two outstanding questions, Dr. Gulick.

DR. GULICK: Thank you.

And the agency, Dr. Nguyen wanted to address the question of reversibility of renal abnormalities.

DR. NGUYEN: Yes, thank you, Mr. Chairman.

I just wanted to bring your attention to Slide No. 25 from the FDA presentation.

[Slide.]

That is nephrotoxicity in Study 437. Now, it all depends on how you defined nephrotoxicity and how you defined reversibility of nephrotoxicity, but based on what we defined, that is, if a patient got an increase in serum creatinine greater than 0.3 or equal to 0.3, and

subsequently, during follow-up, the serum creatinine would decrease down to less than 0.2 or equal to 0.2, then, suddenly you can see the number, the proportions of patients in the two adefovir treatment arms with respect to resolution of serum creatinine, 77 percent in the adefovir 10 mg had that type of resolution versus 39 percent in the 30 mg.

Now, if you set that resolution, the threshold a little bit higher, say, 0.3 or 0.4, then, certainly the numbers will change, but we just wanted to bring to your attention that subtlety, so that may be why Gilead's numbers appear to be much more positive, because I think the threshold was set a little higher, 0.3.

DR. GULICK: So, just as a follow-up question, so you are saying in people that elevate greater than 0.3, if they resolve to less than 0.2, it is about 13 percent who don't do that by the Slide No. 25? I am sorry, in the 10 mg.

DR. NGUYEN: In the 10 mg, you can say that 13 patients or 4 percent of them actually had a creatinine increase greater than or equal to 0.3 from baseline, and among the 13 patients, 10 of them actually had serum creatinine is subsequently

decreased to equal to 0.2 or less than 0.2, so that we could consider as resolved.

DR. GULICK: So, that would be 13 percent who didn't resolve in that group.

DR. NGUYEN: Right, exactly--23 percent did not resolve. I couldn't do that calculation quickly.

But in Study 438, we did not comment on it because a number of the patients with creatinine abnormalities was relatively low, but if you turn over to Slide No. 33, for Study 435, you can see that the proportion of people--I am just talking about cohort A only because of the confounding factors in cohort B--so just look at cohort A only.

You can see that our threshold for resolution is set a little higher now, we are setting at 0.3. So, you can see that 86 percent of patients who had the abnormality in cohort A, did not achieve resolution at the last follow-up time.

DR. GULICK: Just to clarify, Carol, when you mentioned that 100 percent had resolved, it was a different cutoff in terms of resolution.

DR. BROSGART: Right. I thought you were asking, Trip, about patients who had greater or equal to 0.5, and the patients who had greater or

equal to 0.5 all did resolve, but in the patients who had greater or equal to 0.3 mg/dL increase in serum creatinine through week 96, there were 29 patients.

Twenty of these resolved to less than or equal to 0.2 while continuing on adefovir 10 mg. Eight patients remained stable at the greater or equal to 0.3 range, which would have been a 0.3 or a 0.4. It didn't include anyone who was greater or equal to 0.5.

They were stable, so they weren't changing, but I think it is important to know that 5 of those 8 were patients who began adefovir in Year 2, so they have been on placebo in Year 1, and we reset their baseline for where they were on the first day right before starting adefovir 10 mg. All of their baselines were higher than their prescreening baseline or their entry, and if we used either their entry baseline at day zero, back when the study began, or if we used their screening, they were either at or below their screening or baselines values when they had this 0.3 increase.

DR. GULICK: Okay.

DR. BROSGART: And then the other patients

who had the 0.5 resolved. There was only two, one resolved on drug and one resolved off.

DR. GULICK: So, the observation is that the apparent discrepancy is really just related to what kind of a difference we are talking about.

DR. BROSGART: Right, and we agree that for the 0.3, we were using a less than or equal to 0.2.

Open Public Hearing

DR. GULICK: I think we will close the question period at this point, and we will move to the open public hearing. We have four people that have signed up. It would be most convenient for us if people could use the mike in the front.

I understand there are some time constraints from some of the people, so the first person we would like to have speak is Rochelle Yedvarb who has signed up.

MS. YEDVARB: Hello. My name is Shelly Yedvarb and I am from Plantation, Florida. Gilead Sciences arranged for me to be here today. I need to tell you that there was nothing that would have stopped me from being here today because that is how important it is for me to tell you my story.

The fact is I would not be standing here

today talking to you if it wasn't for adefovir, and for my wonderful Dr. Eugene Schiff. One year ago, in March, I became very ill with hepatitis B. I had broken through the Epivir and had a severe case where my liver started to shut down and I was just moments away from a liver transplant.

For the last 16 months, I have been able to have my life back and experience my life with my husband of 33 years, my two children, my son-in-law and my brand-new granddaughter Gabrielle, who is 18 months old.

I have appreciated life thanks to adefovir giving me back my life. Having lost my own mother when I was pregnant with my daughter, it was very important for me to be around for my daughter when she had her child. I didn't want her to miss out on what I missed out on. Adefovir made it possible for me to be here for her and my son and husband, as well.

But, first, let me tell you a little bit more about how I got to that point. It is believed that I contracted hepatitis B as a child, about 10 years old. There are some theories about how I got it, but I was quite young.

I lived with this disease for

approximately 18 years before I even knew I had it. I had some symptoms, but I was not aware what they related to. My first major episode occurred after my son was born when I was 28 years old. I was very, very ill, and I was unable to care for him and my young daughter for quite some time.

It took a year until I was back functioning normally again. During that time, I had learned I had hepatitis B. I was hoping that I would recover, but unfortunately, I was one of the 10 percent who ended up with chronic hepatitis B. The virus never left my system.

I was able to adjust and live with the symptoms, but, in the meantime, I lived my life, raised my family, worked as a psychotherapist, taught at a local community college, and did community service work. I worked hard, but some days I didn't feel really very well at all.

I had symptoms of hepatitis, persistent hepatitis, I was tired, irritable, I had edema, I had insomnia. As a matter of fact, I couldn't remember the last time I had a good night's sleep for a very long time.

But there was no treatment for my disease. I would have bloodwork, I would have ultrasounds, I

would be followed by my physicians, but nothing could be done.

In 1997, my enzymes started to elevate and I went for a liver biopsy. At that time, it was learned that I had cirrhosis of the liver from hepatitis B.

I had done everything right. I had a good diet, I abstained from alcohol, I rested, I did everything I was supposed to, and I was just getting sicker. I was pretty devastated at the time. My daughter was about to get married, I was supposed to be happy. We had a lot of exciting events happening, but I must tell you I was pretty sad and pretty scared.

Shortly after that, I was put on Epivir, but the relief from Epivir only lasted a short while, and about two years after that, and that was 16 months ago, my worst fears materialized. I became sicker and sicker with hepatitis B. The Epivir no longer worked.

I became resistant and had a very severe case of the virus. This was 16 months ago. My granddaughter was just born, I was working full time seeing about 40 therapy patients a week. It was hard for me to tell what was wrong because my

symptoms sort of were similar to just being exhausted. I had bloodwork at the time and discovered that my enzymes were over 700, my hepatitis B was back with a vengeance.

I called the University of Miami and went to see Dr. Schiff immediately, who immediately recognized what had happened. He began to check my blood daily to see if it was just a fluke, the tests were just a fluke. One week later he was able to get me into the trial for adefovir.

He was quite confident that if I got onto this medication, that I would be better and it would work. I was told at the time to go home and rest and wait and see. They said that it would take between 22 and 26 days to know if the medication would turn the virus around.

Meanwhile, I was sick in bed, unable to do anything, and I was monitored every other day with bloodwork as my enzymes began to climb higher and higher and higher, and at some point, I don't think Dr. Schiff even told me what they were because he didn't want me to get any more frightened than I was, because they were pretty high.

I didn't improve in the first 21 days, and I was put into the hospital for a transplant. I

will never forget the day, sitting, getting my blood taken for the transplant surgery when they took 20 tubes of blood and were trying to match me for a new liver.

I went into the hospital jaundiced and very close to liver failure. On day 24, I was admitted to Jacksonville Memorial for a possible liver transplant, I didn't know what was going to happen. I only believed I had a few days to go. That is when the miracle happened. On day 24, my enzymes went down from 3,000 to 1,800. The adefovir was working. It stopped the virus from replicating.

I got my life back you see with no transplant. I would live with my own liver, I would recover. See, adefovir is my miracle drug, it's my wonder drug. My liver functions, in several months, went back down to normal. I had no sign of the virus, a virus I have had all my life. There is no trace of it right now. On one little 10 mg pill a day, I have so much help.

For 15 months, I have been involved with my family and friends, I have been back at work with my patients. I am actually able to travel and do anything that I want, the adefovir keeps

working. I have my life back. I get to be with my husband, my children, my grandchild, have fun, have my life.

I want to thank everybody here who was involved in developing this drug. Without it, I wouldn't be here, and this is what I believe. Everybody deserves a chance to get better, to recover. I am so lucky. This drug needs to be available to anyone who needs it, so they could have their life back.

By the way, I had no side effects, no symptoms. I feel stronger and better than I ever have in my life. Actually, what I have learned in the last year is what it really feels like to feel good, because I don't think I ever really knew. I have more energy and more stamina than I ever imagined possible.

The only side effect I have - optimism, optimism that this will work for me for a long, long time.

Thank you for this opportunity to speak.

DR. GULICK: Thanks very much for sharing that with us.

The next person to sign up is Elias Anastasopoulos.

MR. ANASTASOPOULOS: Good afternoon, everybody, ladies and gentlemen. Thank you for this opportunity for me to be here today as an expert of sorts, an expert because I have a fault habit, I just be here for half of my life.

I was born in Greece in 1942. I immigrate when I was only 15 years old. I live in Montreal for 15 years, which I grew up. That's where I found my wife and I married, and I have three beautiful kids.

I went to school and became a French chef, which with that I did open many restaurants and I was very successful until I became 30 years old. I moved to Daytona Beach. That's when I discover that I had that virus, that virus which has been with me for 30 years.

I felt extremely fatigued when I really had the symptoms, and went to a doctor, a friend of mine, which was trying to find out what was wrong with me for three months. He couldn't tell what kind of sick I was, why I was sick.

Finally, I went to Gainesville, Florida. That's when they told me that I had hepatitis B or, in those days, they didn't know exactly. They told me non-A, non-B, they weren't sure. Thanks to a

family friend that I have in Miami, he introduced me to Dr. Schiff.

Well, I am sorry, but every time I mention that name, tears come in my eyes. I could call him as a small God, and my priest, he told me that's okay, you can call him a small God.

Well, he explained to me in bare terms what was that virus, not only I had hepatitis B virus, but I had a very weird virus. As he explained to me, it was not the common virus that we know about. Well, he asked me to go every six months, and I know Dr. Schiff now for 28 years.

Until 1993, we thought we were doing okay although I was weak, but I was doing okay. That's when the virus came, and we had a severe attack. I felt extremely weak, like never before. My liver getting extremely damaged, and we will not stop it, we couldn't stop it.

They put me on three rounds of interferon. For several months, I was very sick, I reacted terribly. We couldn't do nothing to stop the virus. In my opinion, interferon made it even worse. This is what I believe today.

In April 1994, we couldn't wait anymore. Then, I had a liver transplant. At that time, they

weren't doing many transplants for hepatitis B, because they were afraid that the virus would come back. Dr. Schiff felt we had the only chance to treat it with immunoglobulin. By the way, that medication was very expensive, but I would pay it again just to be here.

Dr. Schiff thought with doing that and have the transplant, we had a good chance, and he was right. At that time, the well-known transplant surgeon Andreas Tazakis had joined the team at University of Miami, and they performed the surgery on me. I had a liver transplant April the 10th.

At first, even after some rejection complications and some problems, I thought that we had the virus under control, but only for a few months, the virus reappeared, came back to me, stronger than ever.

The outlook seemed very grim, and it looked like we were at the end of the rope. Dr. Schiff then decided then that I had to become the first liver transplant patient to try lamivudine, the first, as he told me, in the whole world, not only in the United States.

Nobody can imagine how happy I was after going through the transplant, and a few months

later I was thinking that that was it. I did all this for a few months of life. Well, I had the lamivudine and I felt good. I felt good for about two and a half years.

Then, I find out that the virus was coming back very strong. I remember the day that my surgeon, Dr. Tazakis said, you know, "Elias, I am getting ready for the second time around for another transplant."

Don't misunderstand, I would go 10 times, I love life, but that is not something that anybody should go through. It is very difficult, very hard. Many more other people went on that medication, lamivudine, and they did much better. In fact, I have heard of people that they still go on for five, six years. I wasn't that lucky, I only had about three years and a half.

Soon thereafter, when the doctor told me about the other transplant, he says, "Well, we have one more hope. We will ask Dr. Schiff if he could do something about it," and I will never forget that day when we call your office, Dr. Schiff, you were in Venezuela.

I said, "Well, how could he do all that by being in Venezuela," and your office told me he

could do it just the same by being that far away.

Well, we had biopsy then and the doctor says to me, "Well, you have fibrosis," and Louie said, "You don't have long." And I know in a few days after that, they call me and they had good news, that I was to have the new medication, this medication which it is a miracle.

Since that, it was sometime in 1999, springtime, in a few months I felt the difference when my HBV DNA and ALT levels were dangerously high, soon after taking that medication, my level declined and after several months, the virus was undetectable.

Now, you all can imagine when the nurse told that there is nothing, we couldn't find the virus. Are you all familiar with the Greek dance? I did it.

That's the first time after 30 years, I can tell you that I feel human again, I feel good. There are days that I don't even think about what happened to me, because me body helps me to say, well, there is nothing wrong with you, there is no fatigue, I don't even feel that I have to sleep because normally, I sleep only 5 hours every 24 hours.

When I was sick, I did 10 hours. When I go more than 6 hours, I know that I am sick, and Dr. Schiff, believe me, I only sleep 4 hours now, I feel strong.

You say about side effects. Well, the nurses prepare you and the doctors, that since it's a new medication, there will be some side effects. I never care about it, I said keep me alive, and I don't care about side effects.

Well, I want you all to know that with this medication, there is absolutely no side effects, there is no nausea, I don't feel anything. I take it just like an aspirin, I don't think about it, and it has no side effects.

I feel normal. Because of this drug, I can hug my kids, my grandkids, and they don't feel sorry about me anymore. They look at me that they have a healthy father and a healthy grandfather. I would like to be a proof to the other people and other, you know, sick people with hepatitis B, to see that there is life, there is future.

I would like to convince this committee to approve this drug, so others can benefit like I have. I can say one thing. You know, every time I go to that clinic, Dr. Schiff, I see many people,

that they have been there for quite a few years, because we have to go every month, and the thing that makes me sometimes confused, I don't know what to think. I am guilty, I am alive. Many faces that I have seen in your office, that is no longer around with us, and I keep asking myself if that drug had come out two, three years ago, or five years ago, if this opportunity had been given to everybody, I think I would have seen their faces around.

I am confused, you know, I don't know. I am lucky. I am guilty because I was one of them that I am alive.

I am fortunate to see seven grandkids growing up. I wish I had a picture, which I only had them after I got the transplant and I have that medication. I am playing with them. Life is back normal to me.

I beg you, please give this opportunity to many other people. They are waiting to have this medication.

With this, I finish today. Thank you that I had this opportunity to talk in front of you, and, please, have this medication available for everybody, special to some countries like where I

was born in Greece, there is about 10 percent of the people affected with this virus. If this virus get all over the world, how many people will that benefit? I bet you.

Thank you.

DR. GULICK: Thank you very much.

Next to sign up to speak is Larry Kramer.

MR. KRAMER: Good afternoon.

My name is Larry Kramer. I am a writer. I am the cofounder of Gay Men's Health Crisis, the world's first AIDS organization, and I am the founder of Act-Up, the protest group.

Needless to say, I am not accustomed to appearing on behalf of any drug company. I have paid my own expenses to appear before you today to testify in behalf of adefovir, which I consider to be a wonder drug, and which I believe helped to save my life.

I tested HIV-positive in November 1988 although I believe I was infected at least 10 years earlier. I believe my hepatitis B also goes back to the mid-to-late 1970s. In February 1994, I began low-dose AZT, not for HIV, but for my declining platelets for which it has continued to prove most useful.

In August 1995, I began taking 3TC Epivir for my hepatitis B. In August 1999, I was on vacation in London when I became very sick with a fever of 103 degrees. I immediately flew home only to discover that no reason for the illness could be found. In retrospect, I believe this is when I became resistant to 3TC. The dreadful, malign, and evil GlaxoSmithKline, which I have hated since it was the dreadful, malign and evil Burroughs Wellcome, was finally getting back at me.

I should say that over this period, a persistent cough that I had had so long I cannot pinpoint its commencing became increasingly worse, so that there were days when I could not speak a sentence without hacking. No tests or specialists could define its cause or recommend anything to suppress it. Believe me, I tried everything.

In August of 2000, Dr. Anthony Fauci saw me and told me that I looked sick and he was concerned. I weighed 135 pounds, down some 30 pounds from my normal weight. Indeed, I looked and felt like I was 100. I had no energy or appetite.

He admitted me to the hospital at NIH where two days later I received the news from Dr. Jay Hoofnagle that my liver was in very bad

condition indeed. He told me, as he did Dr. Fauci, of a new experimental drug called adefovir which might be of help to me. In any event, there was nothing else to take.

On October 13th, 2000, I underwent the first of what would be five tappings of my increasing ascites. The first one relieved me of 10 liters. This is what I looked like just over a year ago.

On October 16th, 2000, I started adefovir in an NIH trial under the supervision of Dr. Judith Faloon. My hepatitis B viral load at this date was 8 billion copies per millimeter of blood.

For the next months, my liver functions indicated great trouble. More and more from my various doctors, particularly Dr. Donald Kottler of St. Luke's and Dr. Samuel Seigal of Mt. Sinai, as well as Dr. Fauci, I was hearing the time was running out on my liver. More and more I was hearing that I had just six more months to live.

I accepted this fate and was prepared to die. Early in 2001, Dr. Faloon told me that she believed I might be eligible for a liver transplant. For the first time, transplants were being done on people coinfected with HIV and

hepatitis B. Indeed, the NIH was preparing a protocol to study just these.

She gave me a list of possible transplant centers and firmly suggested I investigate them. She repeated her suggestion on my next monthly visit to NIH for my adefovir. So began the arduous, exhausting, time-consuming task of locating a transplant center that would accept me and investigating whether my insurance would pay for me.

As anyone who has had to deal with an expensive, rare, and life-threatening disease, these are no easy tasks given the state of our entrenched bureaucracies particularly when one has been told he has so little time left to accomplish all of this.

I believe this is where adefovir became particularly life saving. I was now feeling wonderful and full of the energy necessary to pitch right in and fight. So, to repeat, as my liver was evidently deteriorating quickly, my overall health was actually improving.

My taps for ascites were still needed, but my hepatitis B viral load was decreasing. I had been investigating and what I was hearing was

frightening. I might die from such a transplant, too. My initial visits to Mt. Sinai, New York, where I live were not calming. Doctors were unpleasantly discouraging, and it was evident that they were uncomfortable performing surgery on people like me.

Eventually, after much precious waste of time, thankfully, they turned me down. Then, I heard about, and eventually met, Dr. John Fung, the head of the University of Pittsburgh Medical Center's Thomas E. Starzl Transplant Institute.

For those of you who do not know this, Dr. Starzl actually invented the liver transplant, and the Starzl Institute is the parthenon of transplants. Dr. Fung was far more encouraging and supportive of my transplant, and I applied for evaluation and listing there.

Unlike Mt. Sinai and almost every other medical center I have discovered, Dr. Fung believes that the transplanting of the coinfected can no longer be considered an experimental operation.

This has now been confirmed, as you know, rightly in the New England Journal, and he is willing for the rights of the coinfected to now be treated equally. Indeed, in rapid order, I was

accepted for listing by Starzl and Medicare and Empire Blue Cross approved me for a liver transplant.

As I said, the closer I was getting to my transplant, the better I was now feeling. I was gaining weight, and my energy was strong. I was feeling so good that I was wondering if I should put off the transplant perhaps indefinitely, that if I stayed on the adefovir, which was obviously why I was feeling so much better, perhaps in addition to reducing my ascites and my hefty viral load, it would also cure the cirrhosis that was causing my rampant end-stage liver disease.

Wisely, I was advised not to be so casual, that adefovir has not yet accomplished that. By the time I left the NIH adefovir trial in October 2001 to transfer to the one at UPMC, my hep-B viral load had decreased to 4,000 copies per millimeter of blood.

By the time I left the NIH one year after starting adefovir, there was no ascites in my system as per an ultrasound there. I had my liver transplant on December 21, 2001. Dr. Fung said the old one was truly on its last legs.

I was the 22nd coinfected person to

receive a new liver, and at 66, the oldest person. I believe my transplant is considered to be a great success. I do know that each and every single day, I feel wonderful. My awful cough disappeared the minute I came out of the operating room. My HIV viral load and T cell count continue approximately what they had been before, almost undetectable for the first and in the 400s for the latter, although now I must take the dreaded cocktail.

But because I am HIV-positive, I require next to no anti-rejection drugs, the only benefit I have found from being HIV-positive, and there is no detectable hepatitis B in my system. No one will say that it has gone from my system completely, but no one will say it hasn't, and I am still on my daily dose of 10 mg of adefovir.

I received the liver of a 45-year-old man. Dr. Fung and his fellow surgeons say in all seriousness that we are as old as our livers, and he thinks it possible I have another 20 years of life. Indeed, I feel 45 at most.

Thank you, Drs. Fung, Fauci, Faloon, and Kottler, and thank you, Gilead, for saving my life.

Has anyone got any questions?

Thank you.

DR. GULICK: Thank you very much.

Our final person to sign up is Alan Brownstein

MR. BROWNSTEIN: Thank you very much.

I am Alan Brownstein. I am the President and Chief Executive Officer of the American Liver Foundation.

ALF is a national voluntary health agency dedicated to preventing, treating, and curing hepatitis and other liver diseases through research, education, and advocacy. We are made up of patients and families as well as medical and scientific leaders organized through chapters throughout the United States.

I am here today to talk about hepatitis B and to share with you the personal stories of patients who have been afflicted with chronic hepatitis B.

We are pleased that you are reviewing the new drug application for adefovir for the treatment of chronic hepatitis B. We are not here today to speak to the safety or efficacy of adefovir, but rather, to speak to the urgency concerning chronic hepatitis B and the need for expeditious review for all therapeutic agents considered for the treatment

of hepatitis B.

As you know, hepatitis B is a major cause of chronic hepatitis, cirrhosis, hepatocellular carcinoma, and that there are more than 1.2 million Americans with chronic hepatitis B infection, and an estimated 15 to 25 percent will die of related complications. As you also know, there are about 6,000 deaths each year as a result of chronic hepatitis B.

In the U.S., the incidence of hepatitis B has declined dramatically from 450,000 per year in the 1980s to 80,000 per year at the dawn of the 21st Century thanks largely to effective public health immunization programs. However, this 80,000 number must be coupled with the underlying prevalence of hepatitis B, over 1.2 million, along with the high prevalence and associated incidence among new immigrants especially from select Asian populations.

At this time, alpha-interferon and lamivudine are the only FDA-approved therapeutic agents known to have a lasting beneficial effect in the treatment of chronic hepatitis B. Interferon has been known to produce long-term remission in about one-third of selected patients.

With lamivudine, management of chronic hepatitis virus, the hepatitis B virus, has been initially successful in 20 to 30 percent of patients. The problem, however, as has been discussed, is that resistance occurs in about 15 percent of treated patients each year after they are treated.

Thus, there is a dire need for more treatment options for patients with chronic hepatitis B who do not respond to interferon therapy or who develop lamivudine resistant strains of the virus. Without further therapy, many more will go on to die, and the more fortunate will receive liver transplants.

We are optimistic with the development of additional anti-viral therapies, one of which is adefovir, you are reviewing today. We are hopeful that adefovir, for those of whom neither interferon nor lamivudine was sufficient, will help a number of patients who did not respond to either of these agents.

We are grateful that you will be giving all of your attention to this in your review of the scientific data here today. We are also grateful that you have planned to conduct an overall

scientific review about therapeutic agents for hepatitis B tomorrow. We think that's great.

We understand that there are several new drugs and therapeutic approaches being developed as therapy for chronic hepatitis B. Also of great importance are the exciting new developments in the treatment of hepatitis C that are on the horizon.

We hope that this committee will take into account the pressing need for new treatments for both of these forms of chronic liver disease when evaluating these new approaches and working with their manufacturers. It is our view that it is critical to streamline the process of approval for new drugs and we appreciate and we are grateful that you appreciate the importance of expedited review here.

In closing, we thank you for your attention to hepatitis B and your understanding that there is a critical need for new therapies, a critical need that needs to be addressed now.

At this time, I would like to take the opportunity to share with some excerpts of letters from people in different parts of this country who suffer from hepatitis B, including one from Dr. Timothy Black, President of the prestigious

Hepatitis B Foundation. Photocopies of the complete letters are included in your packets and for inclusion in the record.

Dr. Timothy Block, President of the Hepatitis B in Doylestown, Pennsylvania, writes: "...there are more than 400 million people worldwide who are chronically infected with hepatitis B virus, with as many as 1.25 million in the U.S. alone. These individuals will not benefit from conventional vaccinations, which are so useful in preventing chronic infection. Since chronic infection with HBV can lead to life-ending cirrhosis and liver cancer in as many as 20 to 40 percent of those infected, as many as 100 million will die from serious liver disease without effective intervention."

Mr. James V. Hosman of Arkansas writes: "Hepatitis B patients must face each day knowing that their condition is a killer and could take a turn for the worse at any time. This makes our condition very emotionally exhausting as well as physically tiring. The only hope that hepatitis B patients, like myself, have is that new and effective treatments will be developed before it's too late for us."

A liver transplant recipient Mr. Edward Petraiuolo of New Haven, Connecticut, writes: "Without the ongoing research that is conducted to prevent and control HBV, I would not be alive today. Medication has been developed that keeps my condition stable so that I can enjoy a relatively normal life after transplant. However, further therapies must be developed to bring this disease under control so that transplantation won't be the only remedy."

Mr. Edmund J. Blake, another liver transplant recipient living in New York City, writes: "...my condition deteriorated to the point that in June 1993, the prognosis was cirrhosis, cancer or even death. After waiting six months, I received a liver transplant in December 1993, about the time when I was told I had only a week or two to live.

If a drug is successfully developed and utilized soon to remedy chronic hepatitis B, thousands of lives may be saved, with considerable financial savings from the costly procedure I went through of over $500,000. The need is great, the time is short."

Finally, there are some thoughts from Mary

Gong Sweeny of Rochester, New York. Ms. Sweeny lost her brother and mother to hepatitis B. She writes: "It has now been 17 years that I have known that I am a hepatitis B carrier. I first became aware of this when my brother became ill in 1985. He had primary liver cancer. As a result of hepatitis B, he was told that he had a short time to live, and two and a half months after diagnosis he was gone. His doctors strongly suggested that all family members, direct and indirect, be tested. It turned out that we were all, all of us were positive. Two and a half years later, my mother became ill, and once again, two and a half months later, she was gone."

"I appreciate your efforts to review this drug," she writes, "and I do hope that other choices for antiviral drugs will be available choices for me in the future. My future may depend upon it."

Those are some of the faces of hepatitis B throughout America.

I appreciate you allowing us the time to share those voices with you today.

Thank you.

DR. GULICK: Thank you very much.

That concludes the four people who signed up for the open public hearing.

Is there anybody else who would like to make a statement, who did not sign up?

[No response.]

DR. GULICK: We will go ahead and close the open public hearing part of this meeting.

At this point, we are ready to receive our charge.

Charge to the Committee

DR. BIRNKRANT: If we could turn to the questions, there are five questions that will be posed to the committee today. The first three require a vote.

The first question deals with the safety of adefovir 10 mg in patients with chronic hepatitis B. As the committee approaches this question, we would like them to also discuss specifically the use of adefovir 10 mg in patients with decompensated liver disease and those with baseline renal insufficiency.

In this question dealing with safety, we would also like the committee and consultants to comment on proposals for monitoring adefovir-associated nephrotoxicity and the

situation with regard to discontinuing adefovir and patients developing hepatic flares.

The second question deals with efficacy of 10 mg of adefovir for the treatment of chronic hepatitis B. So, in addition to general comments and a general vote on this question, we would also like you to discuss the efficacy in patients with compensated disease, decompensated liver disease in the setting of lamivudine-resistant disease, in the setting of presumed precore mutant disease, and in coinfection with HBV and HIV.

Question No. 3 involves a risk-benefit discussion, so based on the discussion for Question 1, safety, and Question 2, efficacy, we would like the committee to discuss the risk-benefit profile of adefovir 10 mg.

Based on the outcome of the votes, we will proceed to Question No. 4. Question No. 4 deals with product labeling and in that question, we would like committee input again for monitoring for renal toxicity, perhaps monitoring following discontinuation of therapy, as well as perhaps the committee could comment on the length of treatment in the setting of e-antigen seroconversion, however, we may touch on this more tomorrow.

Lastly, we will be asking you about Phase IV commitments, that is, the conduct of studies following approval.

Thank you.

Committee Questions/Discussion

DR. GULICK: Thank you, Dr. Birnkrant.

Committee members, let's take the first question first, which is once again: Has the applicant demonstrated the safety of adefovir 10 mg daily dose for the treatment of chronic hepatitis B?

Let's consider that as a general question and then we will take up some of the specifics after some discussion.

Who would like to start? Thank you, Dr. Wong.

DR. WONG: The answer to the general question is yes, they have demonstrated safety. I think that the safety is patients with decompensated liver disease, there is some information, but it would sure be nice to have more.

Safety in patients with baseline renal insufficiency, I think there is just not enough safety data that we saw today to really make much

of an assessment there. This really seems to be a question that is in the process of being studied or plans are in hand to begin a formal study, but I think we just don't know yet.

DR. GULICK: Yes, Dr. London.

DR. LONDON: I think there is an unanswered question about whether renal toxicity is cumulative, such that there might be very low levels of impairment over many months or years, and since this drug is likely to have to be taken for a long time, I think that that is something that just needs to be kept in mind. I don't think it is a reason to not approve the drug, but I think it is something that really needs to be considered.

I was not totally reassured by the presentation of the data today that that would not occur.

DR. GULICK: Dr. Hollinger.

DR. HOLLINGER: I would agree with Tom that clearly it appears to be safe for 48 weeks, in my opinion, and I just don't think you have enough data over time to know whether this has some toxicity to mitochondria or other things in the kidneys and unfortunately it looks like, for the vast majority of patients, if they are going to

take a drug like this, it will have to be taken for a real long time.

The outcome, what we all want to look for is a remission. There is going to be a very few that are going to actually get "cured" or become HBsAg-negative, as was true for lamivudine, probably less than 2 to 5 percent if you compare it with a placebo group, and the seroconversion rate from HBe-antigen-positive to HBe-antigen-negative also is fairly low in these patients. I think it was like 6 percent if you again subtract out the placebo group.

You do have a little bit higher level of effectiveness for the loss of e-antigen, but in terms of safety, because of all that, it looks like the largest majority will have to be treated for several years, and that data is just not available and clearly needs to be monitored very closely.

DR. GULICK: Other thoughts, Dr. Fletcher?

DR. FLETCHER: Based on the long-term safety part, unless I am misinterpreting the analysis from the FDA, I am referring to Slide 27, I think it provides data that there is an increased risk of nephrotoxicity with longer term therapy.

Please correct me if I am misinterpreting

these data incorrectly, but it says at week 96, 9 percent in Study 437 and 10 percent in 438, and if at 48 weeks, that risk was something around 2 to 3 percent, then, these rates could be double to triple after one additional year in terms of the rates of nephrotoxicity.

So, while I agree with the points that have been made about week 48, that therapy looks quite safe, it does suggest with longer term therapy, that there is an increased risk of nephrotoxicity.

DR. GULICK: Dr. So.

DR. SO: I am also concerned about the long-term safety and nephrotoxicity issue. I was just actually calculating some of this on the plane, and I figured based on the table provided from Gilead, page 54, there are about 4.4 percent of the patients on 10 mg/day, which experienced elevation of creatinine over 0.3.

As the FDA analysis on Slide 27 showed that at 48 weeks, actually, at 96 weeks, that number could have increased to about 9 percent, but more concerning is the number, you know, based again on the Table 19, about 1.4 percent have unresolved, so-called "unresolved" elevation, so

these are patients I presume have suffered some permanent renal damage.

Once again, this is a disease which affects 400 million people, and actually, a lot of these people are actually in Asia. So, I would say that a lot of the drugs being used are going to be in Asia, and a lot of these people might not be actually followed up very closely by the physicians.

So, if you figure, if you treat a million people with adefovir as primary therapy, I am concerned that based on just the short-term analysis, you know, 14,000 of them will have some unresolved renal dysfunction. To me, that is concerning, but on the other hand, I feel that adefovir definitely seemed to have a real--and the cost-benefit ratio may be different in those who are lamivudine-resistant, who has a lamivudine-resistant HBV, but I am concerned about this drug in the long term as a primary therapy for chronic HBV because of the uncertain long-term nephrotoxicity.

DR. GULICK: Dr. Kopp.

DR. KOPP: If I could make an argument as a nephrologist that I am actually more reassured

about the relative safety in terms of patients with baseline normal renal function. We saw that in one study, 5 percent versus 2 percent of placebo had elevated creatinine, but the numbers were reversed in the second study, 438, and that most of these patients resolved even though they continued on a lower dose

So, I guess I am more willing, I realize that it is not without any renal side effects, but I am thinking ahead already, maybe I shouldn't be, to the issue of cost-benefit, and thinking that in those with baseline renal insufficiency, who are closely monitored, which is another part of this question that we need to come to, that the safety is acceptable as I see it.

Do you want to talk about monitoring now or should we leave that?

DR. GULICK: Let's hold that for a minute, but we will get back to that.

Dr. Sjogren and then Dr. Sherman.

DR. SJOGREN: I kind of agree with some of my colleagues that the long-term therapy is still perhaps not well delineated, and the safety. However, I want to temper my comments, because I do think that people with decompensated liver disease

and with baseline renal dysfunction need this medication perhaps more than other people that have well compensated liver disease, who have very early damage in the liver.

So, like we heard from some of the people that had the testimony before us, if the FDA would not approve the drug, perhaps in a limited kind of a scope, I don't know, that is something that the agency will have to decide, and with very close monitoring, some people may benefit from the drug, particularly because they have renal dysfunction to begin with or because they have decompensated liver disease, they may be left out, and that would be a disservice to our patient population.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: As someone who frequently deals with patients with chronic hepatitis B, I am very cognizant of the need to assess the risk-benefit ratios of any drug that is used. The renal toxicity clearly has the potential to be an issue over extended periods of time.

That said, hepatitis B is a serious and progressive disease, and the drugs that we have today are less than optimal, and having also cared for a number of patients who have had significant

flares with lamivudine breakthrough and required hospitalization from that, I could say that restricting a drug like this to a secondary use would not be the choice that I would make.

I think that if we can develop appropriate monitoring schemes, that this is a drug that belongs in our primary armamentarium.

DR. GULICK: Dr. Englund.

DR. ENGLUND: I think the investigators have and the company has demonstrated safety of this drug for 48 weeks, and I think that they clearly have not demonstrated it for enough people for longer than that.

I also think it is important for our patients, and as soon as possible, our pediatric patients, too, to have such an agent available because I do think with proper monitoring, that it will be beneficial to actually helping our patients.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: I certainly agree it's safe in people with normal renal function. The groups that I am concerned about, that has been highlighted by previous discussions, are the very sick people whether it's from decompensated liver

disease or comorbidities who may get this drug.

The discussions around dose adjustments for renal insufficiency really don't address a critical issue of potential interactions with other nephrotoxins even if the exposure to adefovir is controlled.

For example, do we know anything about what is the risk if somebody is on an aminoglycoside or amphotericin or foscarnat, any of these other antiviral drugs, some of which have to be chronically given.

In other contexts, we have just said that use of drugs like this should be relatively contraindicated, but I think these kinds of interactions need to be explored in some formal mechanism, because the clinician then has to face the often unexpected decision of which drugs do you stop and which do you avoid in the critically ill setting.

DR. GULICK: Yes, Mr. Grodeck.

MR. GRODECK: What I am concerned about is not so much the kidney toxicities, that it seemed to be fairly predictable, but cessation of the drug if 1 of 4 people who went on to placebo saw an elevation in ALT 10 times normal, that is

significant, and for whatever reason they go off drug, can 1 in 4 people expect it 10 times normal liver function.

DR. GULICK: Dr. Sun.

DR. SUN: Back to the renal issue, I just wanted to remind people that this compound has been studied extensively for another indication, at a different dose, but there is obviously a lot more safety data than is in this particular dose here, so when the agency looks at renal toxicity, I am sure they are going to look at the extensive amount of safety data that was collected in the HIV indication, particularly in patients that may have been followed longer than the data for the hepatitis B indication is currently.

DR. GULICK: Dr. Wong.

DR. WONG: Remember, Eugene, one of the problems with that discussion was that the biggest weakness of the safety database, when adefovir was used for HIV, was we didn't really have much beyond about 48 weeks.

So, the problem of what happens beyond the duration of the study that we have in hand is always going to be there. If they come in with two years or three years worth, we would say, well,

what happens after four or five years. I mean, you know, forever is never going to be able to be answered, but in my view, we have seen this drug twice over a very large range of doses.

There is no question it's a nephrotoxic drug. It looks to me like the dose that has been proposed today really strikes the right balance. I mean it's quite safe for people with normal renal function, its safety in people with abnormal renal function is not yet known, and for the duration of the study that we have in hand, it seems quite clear. For longer periods of time, we don't know, and we are going to have to find out as people are treated for longer periods of time.

But whatever that period is, someone will always say, well, we don't know what it would have been if we had gone twice as long.

DR. GULICK: Let me ask you a question, Dr. Birnkrant. You started off by saying that we would take a vote on each one of these questions. It is my observation that the committee, in considering the safety, information was immediately jumping to the risk-benefit ratio.

So, my question to you is, do you want us to take a formal vote to answer this question,

should I sort of summarize what has been said, and we move on to efficacy and have the vote really be Question No. 3, which is the risk-benefit ratio, would that be acceptable?

In other words, do you want us to take a separate vote on safety, then efficacy, and then the risk-benefit ratio, or should we discuss the first two and move to the third?

DR. GOLDBERGER: If there appears to be consensus on each of the first questions, the first two questions, then, I think it is okay to in some way acknowledge that and move on to the formal vote in the third question.

If there appears to be less than consensus in terms of the overall question, not necessarily the subgroups, then, a formal vote may be preferred.

It seems as though for the first question, I have not heard anyone say anything other than they think fundamentally that it is safe with a variety of caveats, which I think Dr. Wong described pretty well in terms of what you can reasonably expect.

DR. GULICK: Well, if I take your comment at face value, which I guess is what I will do, I

will refocus the committee and say that we will take a vote on this question, and it is going to be the very broad question in yellow up there, has the applicant demonstrated safety of adefovir 10 mg daily dose for the treatment of chronic hepatitis B.

In other words, many people in their responses made some caveats about populations or length of time or considerations, but I am going to ask that question when the discussion is done, and people should evaluate all of those factors and come up with an answer to that question.

So, you are forewarned that that is what I am going to do.

Are there other comments about safety, because I do think we want to touch on the monitoring part of the question next, too.

Dr. Kopp, do you want to help us out?

DR. KOPP: Maybe I could make a comment about the use in elevated creatinine populations. We were shown that something like 40 percent of patients had a further deterioration in renal function, but the key point I think, as you mentioned, Dr. Wong, is we don't know what the placebo group would have had. These are patients

on cyclosporine, FK, getting sick, getting amphotericin, and there really is a deficit in the database there.

On the other hand, we know that, in general, those patients tended to reverse, as well, I can't quote the exact number, but I think we don't have everything we would like to have.

Now, in terms of monitoring, I have to say I was quite uncomfortable to hear the proposal that these patients would just have a creatinine clearance every three months. I could say that there is an easier way to estimate GFR, which is the MDRD or modification of diet in renal disease equation that makes life a little bit easier and that you can just get a BUN and creatinine, and plug it into a formula, and it more correctly estimates, more accurately estimates true GFR than it does creatinine clearance.

I think that would be a relatively small option to change, is an option to add to the clinician, but I do feel uncomfortable even in those with normal renal function in only monitoring them four times a year.

I don't know what the right frequency is, I don't know if it's 4 weeks or 6 weeks or 8 weeks,

but my own feeling is some more frequent monitoring, I think with just a blood test to get serum creatinine would be adequate.

DR. GULICK: Other thoughts about that point?

Dr. Schapiro.

DR. SCHAPIRO: Regarding the monitoring, I think that monitoring creatinine, you know, waiting for the damage to be done, is somewhat problematic. I was hoping to see data correlating drug levels with toxicity. We have models like that for other drugs, and I think that it would have been appropriate, it would have been very helpful for us to see correlation between exposure and to what degree they can prevent those toxicities. I think that would be very helpful in us deciding how to monitor the patients.

DR. GULICK: Dr. Kumar.

DR. KUMAR: In both Studies 437 and 438, patients had to have a normal creatinine to enter into the study, but in the real world, we know that that is really not going to be what we are going to see in the patients, and I think I have some concern on the cumulative nephrotoxicity in other groups of patients as was seen in the transplant

population.

DR. GULICK: Dr. Stanley.

DR. STANLEY: Just to forewarn you, I am going to have trouble voting on safety because of my concerns about the cumulative effect and I concur with my colleagues over here that we are going to have to be very aggressively monitoring, because it is precisely the folks that need this drug that are going to be at the highest risk for nephrotoxicity.

DR. GULICK: Would people like to make comments about the flare phenomenon of discontinuing adefovir, general comments, and then what monitoring we would suggest in that setting would be appropriate?

Dr. Sherman.

DR. SHERMAN: Well, the flare phenomenon is very similar to what we see with either lamivudine withdrawal or lamivudine breakthrough, and as I said before, does constitute a serious clinical problem. Patients have died from this, patients have been hospitalized, particularly those who already have fairly advanced liver disease.

So, I think it is going to be important to ultimately address do patients stop at the end of

the course of where we have the data or will we include something, if this is approved, in the licensing recommendations that, in fact, there should be consideration of continuation based on future data, whether there is a need to taper doses slowly or any other mechanism because I think we will see this flare, and if this is introduced into a large number of people, some of those are going to get quite ill.

That should not stop us from considering the use of such a drug, though. It already exists, that problem already exists with the drug that is available to us.

DR. GULICK: Do you have a proposal for monitoring of liver function tests in the event of discontinuing?

DR. SHERMAN: I think again it should be the expectation with the high numbers that we saw that a significant proportion of patients will bump their ALT levels and that if you had pretreatment liver biopsy data or the clinical evidence that the patient had advanced disease, those are probably the ones at greatest risk that we did not hear data about that, and that following therapy, it would be reasonable to follow liver enzymes and probably PT

as a marker of worsening liver disease and possible decompensation in patients on a monthly or every few months basis, but then the question would be what are you going to do about that, and again there is no data.

The assumption would be you would restart the drug.

DR. GULICK: Other thoughts about flares? Dr. London.

DR. LONDON: Actually, I don't think that we heard anything that is very helpful about when you can discontinue this drug. The likelihood is you can discontinue people who have had a seroconversion, but for the large bulk of patients who haven't seroconverted, it really strikes me as unsafe to discontinue the drug even though I have in the back of my mind the possibility of some cumulative nephrotoxicity. I think the hepatic toxicity is real, nephrotoxicity is a possibility.

DR. GULICK: Dr. So.

DR. SO: I think some of us might have difficulty voting on the safety issues without addressing, you know, some of the issues you might address tomorrow is what is the recommended length of treatment.

At the moment I think in the community out there, it is very confusing. There are some physicians who recommend that patients take eight months of lamivudine and you had better stop it because you might develop mutants. Then, they stop it.

If we are going to treat this disease like HIV as a chronic infection, long term, then, the long-term unknowns is an issue. If we are going to treat it like some of the naive days of interferon, you give them four to six months, and hopefully, the patients either recover or not, then, we can live with the one-year safety record.

So, I think we really should clarify. Also, with the e-antigen-negative patients, you know, they are already e-antibody positive. How long are we going to treat those patients? So, I think it sort of links to how we are going to treat this disease, and unfortunately, there is a lot of confusion out there.

DR. GULICK: Dr. Sjogren.

DR. SJOGREN: I think some of my colleagues are already defining the Phase IV studies that need to be done with the drug. Obviously, you know, like Dr. Wong was saying, we

cannot wait like forever, like to have ideal data, but, you know, it is what it is, and 48 weeks data is not such a small contribution.

I would like to see the other 48 weeks data without the problems and whatnot, but that is real life, as well, and I think, you know, I am constantly thinking about my patients, and to come away without adefovir, I just don't know if I can face them frankly, as a clinician.

DR. GULICK: Dr. Mathews:

DR. MATHEWS: The other comment I would make about the flare issue is a study design matter that perhaps could be deferred until tomorrow, but after seeing this dataset, I am very skeptical, that it should be necessary to include treatment withdrawal as part of a study design in future studies.

DR. GULICK: Dr. Wong.

DR. WONG: I would just like to return to the renal function issue because we were specifically asked about monitoring. I think that the sponsor's proposal to have monitoring every three months is reasonable for people who have normal renal function and are doing well, but it is clearly inadequate for anybody who has abnormal

renal function either at the beginning or who develops any abnormal renal function during the course of therapy.

I can't imagine that I would recommend that those people be analyzed quantitatively any less frequently than once a month. That is just one point.

The second point is that I really was not satisfied with the kind of scientific and database that went into development of that nomogram for dose adjustments. I think that it just didn't convince me that that is ready for recommendation for patient usage at this time.

You know, people are clearly going to have to get some sort of guidance, but a lot of caveats should be put behind anything that we say about dosage adjustments in patients with abnormal renal function, because to base the whole thing on a very limited PK study in a few patients where, you know, someone mentioned before, the peaks in the patients with abnormal renal functions were clearly higher.

The total exposure from the graph that we saw seemed to me to be clearly higher. I just have very little confidence that that nomogram is what we will be recommending a year from now. In that

case, I think we have to be very careful how we phrase it at this point.

DR. GULICK: I think we are going to have some more opportunity to discuss that point in one of the later questions, too.

Dr. Kopp.

DR. KOPP: I agree with your second set of comments. With regard to the first and the frequency of monitoring, if I have it right, in 437 and 438, they were seen every month, and if the creatinine jumped up, first 0.3, and then with the amendment 0.5, they would have been dose reduced.

So, the question that occurs to me is if we see patients every three months, and their creatinine increases after one month, but they are at home and we don't know about it, they will continue on their standard dose for another two months.

There was a statement about how the Data Safety Monitoring Board had approved this, and maybe there is data that led them to see that it would be okay, but I don't see that the study design of 437 and 438 allowed you to test what happens if GFR declines and you keep the same dose for an additional potentially two months.

DR. GULICK: Let me try to summarize our thinking here and then we will take a formal vote.

So, safetywise, it seemed the consensus was that we did think that was safety established for 48 weeks in those patients who started with normal renal function, however, many people made the point that 48 weeks is 48 weeks. There was a certain level of discomfort with the long-term safety data although people really felt both ways, pointing out that this is perhaps the best we have today, other people being more uncomfortable with just 48 weeks.

Dr. Hollinger made the point that treatment with this agent may be indefinite or certainly for years in some patients.

In terms of the normal renal function people, people who start with normal renal function, people were eager to see what happened up until 96 weeks, but then again we don't have that data to look at.

There was more concern about those who start out with abnormal renal function. There was a consensus that there is really not enough data. People were concerned about the possibility of irreversibility of a cumulative nephrotoxicity.

People wondered about some of the plans to address this subgroup of people, such as dose reductions, and then just at the end of the discussion, we began to get into the dose adjustment strategy that has been proposed and what the backup is for that.

There was also some concern in those who had other comorbidities. People felt that decompensated liver disease, there was safety demonstrated, but perhaps not enough for some people. In terms of other issues about renal dysfunction, the fact that other nephrotoxins may come into play and that that hasn't really been addressed.

In terms of monitoring for elevated creatinine, there was a distinction made between those who start out with normal renal function and those who start with abnormal renal function. There was a feel that Q 3 months may not be often enough although we didn't personally review the data that the Monitoring Board had access to.

There was a suggestion that perhaps from 4 to 8 weeks might be more appropriate.

Regarding flares, that this is a serious problem that is seen with other drugs, that it

appears to be common based on the data we saw, and then a suggestion that liver enzymes and protime be monitored Q 4 to 8 weeks with the possibility of drug tapering being explored as another way to look at that.

I warned everyone that we are going to take a formal vote, and the question to the committee is, once again: Has the applicant demonstrated the safety of adefovir 10 mg daily dose for the treatment of chronic hepatitis B infection?

Three members of the committee are actually ineligible to vote, and that is Dr. Sun, Mr. Grodeck, and Dr. Sherman.

So, I am going to ask everyone else. I am going to ask you for a yes, safety has been demonstrated, or no, safety has not been demonstrated. We will start with Dr. Wood.

DR. WOOD: Yes, safety has been demonstrated to 48 weeks.

DR. GULICK: DR. KOPP.

DR. KOPP: Yes.

DR. GULICK: Dr. Kumar.

DR. KUMAR: Yes.

DR. GULICK: Dr. Schapiro.

DR. SCHAPIRO: Yes, to 48 weeks.

DR. GULICK: Oh, people are making caveats here. Let the agency note the caveats being made, but try to stick to a yes or no, and weigh all the data.

Dr. So.

DR. SO: Yes.

DR. GULICK: Dr. London.

DR. LONDON: Yes.

DR. GULICK: Dr. Englund?

DR. ENGLUND: Yes.

DR. GULICK: We lost Dr. Stanley. We will come back to her.

Dr. Fletcher.

DR. FLETCHER: Yes.

DR. GULICK: Dr. DeGruttola.

DR. DeGRUTTOLA: Yes to 48 weeks.

DR. GULICK: Dr. Hollinger.

DR. HOLLINGER: Yes, 48 weeks plus the caveats that you had in your summary.

[Laughter.]

DR. GULICK: This is getting longer at this point.

Dr. Sjogren.

DR. SJOGREN: Yes.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: Yes.

DR. GULICK: Dr. Wong.

DR. WONG: Yes.

DR. GULICK: Dr. Stanley stepped out. So, I guess she doesn't get to vote on this question unless she comes back right now.

And the Chair votes yes on this question. Again, just to point out to the agency that many members who voted yes had caveats about the 48-week length of the data.

For the record, that was 15 votes yes, caveats as explained by the individual, and zero votes for no.

Let's turn to our second question.

Has the applicant demonstrated the effectiveness of adefovir 10 mg daily dose--

DR. STANLEY: What?

DR. GULICK: Sorry you missed it, Sharilyn.

DR. STANLEY: What was it?

DR. GULICK: We took a vote.

DR. STANLEY: Abstained?

DR. GULICK: Absent actually--demonstrated the effectiveness of adefovir 10 mg daily dose for

the treatment of chronic hepatitis B? We are asked to consider a number of subgroups including compensated liver disease, decompensated, lamivudine resistance, presumed precore mutation, and HBV/HIV coinfection.

I would like people to start just with an overview of the effectiveness question, and then we will get into subgroups.

Dr. Hollinger.

DR. HOLLINGER: I will take a stab initially. I mean clearly I think that where it really looks I think very exciting and important is in the lamivudine-resistant patients. This, I think really has some real benefits and one that many of us have been waiting for.

The other thing which has been I think quite unique, and you heard some comments from patients today, has been in the group with decompensated liver disease. I mean we saw this with lamivudine also, but you see it here with the adefovir, as well, in some really pretty dramatic changes, which clearly you could not have with interferon because of its decompensation itself.

Then, the other question that I have is the difficulty, the rest of it is really what is

effectiveness. If you take what they have stipulated as their primary endpoint, then, there is some effectiveness. My personal feeling is I am not sure how biologically relevant it is.

There are clearly some changes, and they are statistically important, but we don't really have a long enough period of time to say how effective or how this is going to alter the natural history of the disease.

We can certainly say that there have been changes over 48 weeks, but is this going to make a difference down the line. You have heard patients who have already talked about the fact that they had disease, they felt better, but many of them end up with a liver transplant anyway, but it did get them through some very hard times. That is important.

But the biggest issue is how is this going to change things over the long road, and I am not sure we know that at the present time.

DR. GULICK: Dr. Sjogren.

DR. SJOGREN: Yes. I think that I don't have that many problems with the lamivudine-resistant or with the decompensated people. I think I am convinced in my own mind that

it could be a life-saving drug.

I am going back now to the other extreme, or the other starting point of hepatitis B. What kind of patients are we going to treat? Are we going to treat everybody that is surface antigen-positive, DNA positive, and that has over 2 times the abnormal ALT? Are we going to require biopsies?

If we looked at the studies that were presented today, the patients were all biopsied. The patients had an Ishak score or was it another score. I forget now. I guess a modified Knodell of 10. What kind of requirements are we going to put on these patients because as the drugs gets out, a bunch of our colleagues are going to treat just about everybody that has surface antigen-positive, maybe even normal ALT. Sometimes we have to yield to pressure from our patients that just want to be treated.

With a medication in which we don't know exactly when would we finish, certainly doesn't look like it is going to be 48 weeks, it is going to be longer than that.

So, my thinking is now in the opposite extreme on who are we going to decide to treat. My

gestalt will be to follow the model that Gilead put before us, people that have demonstrated liver disease histologically, and has some substantial liver damage, and that have a definitive positivity of DNA, and education is going to be the name of the game here.

I am on the Committee for GI diseases, and we have seen horrible things like with Lotronex and other drugs, because of lack of education of the provider. I think that is going to be a very, very serious plea to Gilead, as well as the Liver Associations, that we educate one another in terms of kidney function, in terms of who to put on this drug, how long, et cetera, et cetera.

So, I think those things are going to become extremely important not to damage the opportunity of this drug to do good for some of our patient population.

DR. STANLEY: I think that adefovir has shown effectiveness in a 48-week period and, again, I am not going to ask them to do a two-year period or four years because we would never have enough, as Dr. Wong said, but it kind of feels a little bit like deja vu all over again for those of us that were here during the lamivudine conversations.

At least at that time, there was some evidence, early evidence of development of resistance, but I remember very much sitting through very eloquent patient testimony of how we need this drug right now, and we will deal with the resistance if it ever happens, and it is not really going to happen, and you all give us this drug, and we approved the drug, and now we see where we are at with the situation of resistance.

I don't see a question here on resistance, which I was disappointed not to see a question, so that is why I am raising that right now in the form of efficacy, because I am a pessimist. I have been in the HIV world too long, and you have still got replicating virus. It is not suppressed to undetectable in the vast majority of patients, and you have got blood levels of a single drug on-board.

I just believe sooner or later, you are going to see resistance, and I would like to know where--they say they are going to start looking at combination therapy--but when are we going to start understanding, learning from our experience that you cannot treat many of these viruses with one drug. You have got to start from the point of

combination.

So, when we get to future studies, that is one thing I will bring up again, but I am just concerned because I believe that there have not been good enough resistance studies done long term, where is the 96-week data, and I think resistance will happen. It is just a matter of when will it happen and what can we do to use this drug smartly to avoid that, and not end up in the situation that we are with lamivudine or in the HIV world with some of our drugs.

DR. GULICK: I would like to open resistance as part of the effectiveness question. I think it is well placed here.

Dr. Wood and then Dr. Schapiro.

DR. WOOD: As a non-hepatologist, I wanted to just take a step back in terms of addressing the efficacy issue and ask maybe Dr. Goodman or the other hepatologists who are on the panel, as to if there are any studies that correlate surrogate markers of HBV DNA or histopathology improvement in terms of a change of 2 points in the Knodell score with specific clinical outcomes.

So, if your Knodell score improves by 2 points in response to a specific therapeutic

intervention, you have a specific X amount risk reduction in going on to transplant or to cirrhosis. To me, that is very important in terms of trying to get an overall assessment of the efficacy question, because we do have clear efficacy regarding specific parameters that we can measure, which again I am interpreting our surrogate markers for clinical disease, and I would like to know what kind of correlation there is with specific clinical outcomes, if anybody can address that issue.

DR. GULICK: That is going to be a big part of tomorrow's discussion, but I appreciate your point that it's very important to evaluate what we are also hearing today.

Could we start with someone on the committee who would like to address that? Dr. Sherman. Thank you.

DR. SHERMAN: What you are talking about is sort of the Holy Grail of hepatology, which is if you reduce inflammation, you prevent progression of disease and ultimately prevent the outcomes that we are most concerned about, which end-stage liver disease and mortality, or development perhaps of liver cancer.

I think that, in general, we all believe that that is true, and we have models of inflammation that we can go back and look at from many years ago, related to things like autoimmune hepatitis where we know that effective corticosteroid therapy, reducing inflammation, reduces fibrosis, and a long-term, improved survival.

In the field of antiviral therapy, we have some evidence, it is not quite as secure as that, because we don't have enough good long-term follow-up data that gives us definitive answers about survival.

We would like to. We don't yet. There are studies underway that may answer that question in three years, in five years, in 10 years. That said, there are bits and pieces of information to suggest that decreasing inflammation does reduce progression of disease.

We feel that fairly strongly now from hepatitis C treatment, that good treatment that leads to a sustained viral response, in fact, will halt progression of disease in most patients, and that, in fact, something that was really quite exciting and a new concept in recent years is that

the liver will remodel and improve, and we can, in fact, have a regression of fibrosis in some patients.

The concept that two points is important really came from trying to differentiate an amount, a visible amount of decrease in inflammation that is consistent and, while not totally beyond being a random event or sampling error, is real, and so the concept of two points change developed from that because it was something that review between hepatologists, there was often a high degree of agreement at two points, at one point a lot less so among hepatopathologists reading biopsies, and then again a belief that if you decrease inflammation, you reduce progression of long-term disease.

The Halt C trial for hepatitis C is based on this premise, and again, there was data available leading to the Halt C trial that is very suggestive, but does not fully prove that concept at this point.

I think that in the hepatology community, though, the main concept and the things that probably differentiates us from a lot of our infectious disease colleagues is that these are liver diseases, and liver disease is measured by

inflammation leading to fibrosis, and the progression of fibrosis to cirrhosis, and decompensation is simply a physiologic response to altered blood flow in the liver from fibrosis being there.

So, I think that based on all the data we have available, I think most hepatologists would be fairly comfortable with the concept that decreased inflammation is important.

DR. GULICK: Thanks.

Dr. Schapiro and then Dr. Kumar.

DR. SCHAPIRO: I would like to address the issue of resistance that Dr. Stanley mentioned. I think that the sponsor has shown that over a period of 48 weeks, there are no obvious key mutations that have emerged. I don't think anything beyond that can be claimed.

I don't think that some of the claims from the briefing document actually were substantiated by the data. I think some of the basic things you have to do to look at resistance have not yet been done. I think the sponsor did a lot, but apparently due to technology, which is evolving, some of the basic things which do have to be done have not been done, so I think we have to be very

careful in what we say about this, and I think that is important not only labeling, but for the studies that have to be done.

I think clinicians should be aware of this. It doesn't mean that it is not very effective in patients and that they won't use the drug, but I definitely think we have to step quite a ways back from what has been said here today and to say we don't yet know if there is resistance.

It is encouraging that mutations didn't jump out over 48 weeks, but we don't know what the resistance pattern ultimately will be definitely in patients treated longer, and we need better technology to be able to actually say anything about resistance.

DR. GULICK: Dr. Kumar.

DR. KUMAR: I want to again put back my clinician hat and ask myself in which of my patients with hepatitis B that I have started adefovir can I safely stop the drug, and in the data that was present in 437, only 12 percent of patients seroconverted, that has lost the e-antigen and developed e-antibody.

Even in that group, at least in my mind, it was not clear the durability of response, in

that group, can I be assured yes, it is safe, you can stop the drug, and then in the rest of the group and in the e-antigen group, as a clinician, I have no idea when, if at all, the drug can be stopped, and that is particularly important to me when there is some concern that there may be cumulative nephrotoxicity, so I really would like some clarification on that, if anybody could give it to me.

DR. GULICK: Who would you like to clarify it specifically? Your choices are the panel, the agency, or the sponsor.

DR. KUMAR: Anybody who feels comfortable telling me yes, you can stop the drug, and at this point, you can stop it, and this is besides the issue of the flare that everybody has referred to.

DR. GULICK: Perhaps I could ask if panel members could comment on the safety of stopping in the setting.

Dr. Hollinger?

DR. HOLLINGER: I am not sure that we have all the answers. I think what was presented was if there were 20 patients, some of whom were continued on medications, and other stopped their medication after 48 weeks, that had seroconverted from

HBe-antigen-positive to anti-HBe, and apparently, over a follow-up time period of I believe it was 72 weeks maybe, there was no reversion or reversion back to HBe-antigen positivity or to a loss of anti-HBe, and the suggestion was that these patients have a fairly durable response, and I think that is what was seen with lamivudine, as well, in that type of patient.

The one I am not sure that we have any data on are the ones who just lose their HBeAG and are somewhere in limbo, probably with some anti-HBe occasionally, but never really to that stage yet, and that, I don't think we have any data on, none was presented.

So, you are in limbo at that point about where you are going to stop the medication. We just don't know.

DR. KUMAR: If I could clarify that. So, 88 percent of the patients do not lose the e-antigen or did not develop the e-antibody, only 12 percent in 437 developed the e-antibody.

DR. HOLLINGER: But you again have to take that in context, that for also 6 percent of the placebo group also seroconverted, so the difference between the two is really only 6 percent of those

who were perhaps on adefovir that perhaps the adefovir made a difference.

DR. GULICK: Dr. Wong.

DR. WONG: I have a few comments on the efficacy question that, well, that might be a little bit different from the type people have had so far, because on the first question, I think that the sponsor has quite convincingly demonstrated efficacy for adefovir in patients with compensated chronic hepatitis B.

To me, the histologic changes over 48 weeks were really convincing, and I was especially interested to hear the agency's presentation of the improved fibrosis scores when they used the six-point score as opposed to the four-point score, really convincing me that not only was the inflammation improved, but also the fibrosis was improved.

So, there, no question, right, I think they have demonstrated efficacy.

I differ from what some other people have said about the patients with decompensated liver disease, and I would also add the patients with HIV and HCV coinfection. I think in those patients, I believe this drug probably works, but I don't

believe that the efficacy of the drug has been demonstrated, the primary problem being there were no controls in those studies, and also we were mostly measuring HBV DNA as opposed to liver disease as demonstrated histologically.

So, my answer to the second part of the question is that in those patients in whom the supportive studies were done without contemporaneous controls and without predetermined histologic examination, efficacy has not yet been demonstrated.

The last point on resistance is I agree with some of what Jonathan said quite a bit. As I was listening to the presentation on resistance, I was concerned that maybe we were defining resistance in the wrong way or that resistance was being defined as the ability to demonstrate particular mutations in the polymerase gene that other people have associated with resistance rather than that's a potential explanation for resistance that is observed as we treat people.

As I think back on the presentation, there were patients who were described who had breakthroughs of viral replication while on therapy, and my interpretation of that is that

those patients probably developed resistance.

We weren't able to ascribe that resistance to any particular polymerase gene mutation, but that doesn't mean that they didn't have resistance. That means we can't explain the resistance that they had.

So, I would go back to the first principle that we should try to define resistance in the biological sense first, and then try to find a marker for that or a molecular explanation for that, but if we can't find one, that doesn't mean that there wasn't resistance. That just means we are not good enough at explaining the resistance yet.

So, that would be my take on these questions.

DR. GULICK: Dr. London.

DR. LONDON: I just want to return to what Blaine Hollinger said to lead off this discussion. There were 111 patients who went from adefovir to placebo after 48 weeks, 25 percent of them developed this flare greater than 10 times the upper level of normal. That is big time, that is nothing trivial.

The recommendation of the company that you

just need to monitor these people closely when you stop, I don't agree with. Knowing that that is going to happen, I don't think I could discontinue this drug at 48 weeks.

Also, we don't really have what happens to the HBV DNAs when they stop. It was kind of messed up in the problems that they ran into, but you can assume that the DNAs are going back up to normal or higher than they were maybe.

The point is that this is a suppressive drug, it is not a curative drug, and the question is how long do you have to suppress. It is going to be a long time. It is not going to be one year. I think they have proven efficacy at one year, and the other data that goes beyond one year suggests that improvement continues, but I don't think you can stop this drug, so that all the things that we have said about safety, you really have to keep in mind, because I don't think it is safe to stop this drug at 48 weeks.

DR. GULICK: Dr. Mathews and then Dr. Sjogren.

DR. MATHEWS: A brief comment about the resistance issue. I think whether or not resistance is demonstrated, there certainly is a

significant proportion of patients who either fail initially or fail after initial response.

For example, in the 437 study, only 21 percent had less than 400 copies at 48 weeks among the e-antigen positives, and 51 percent in the other study, that were e-antigen-negative. So, there must be other reasons for this failure whether it's resistance or I think there is evidence that drug potency is a problem.

For example, there was suggestive data that the 30 mg dose had an improved virologic response. There probably is data somewhere from the HIV patients under the HIV development program who were coinfected with hepatitis B on what their virologic responses would have been.

So, I think this whole thing should move us perhaps tomorrow in the broader discussion to look at the whole strategy of treatment, and I think the editorial that Doug Richmond wrote in Hepatology a year and a half ago, tried to frame this question, you know, lessons learned from the therapeutic misadventures with HIV over time.

That is really the reason that I was focusing on this question about what is the histologic response among people who are

undetectable by these current assays, because it seems to me the culprit is the virus, and the response from the sponsor, I think was supportive of that, and that were very few people in either study who failed to respond histologically when they were suppressed for a long period of time.

DR. GULICK: Dr. Sjogren.

DR. SJOGREN: I think it's a balance act. I mean there have been other nucleoside analogs that wiped out DNA, but did great harm to the patients. So, you know, we would like to see 80, 90, 100 percent DNA reduction or disappearance, but it comes at a very high price, so our expectations need to think about what has gone on in the past.

My comment to Dr. Wong's assessment in terms of the efficacy of the drug in the decompensated liver disease, I have a bit of a difference of opinion because even with the DNA, because the company in the Slide 59 showed us impressive data, which I had in my notes to ask them how they explained that, because this is what I would like to see in the patients. These are post-transplant and pre-transplantation, and if you look at it, the reduction of DNA to undetectable levels was 76 percent, and these are sizable number

of patients, there is 128, and in the post-transplant was 186.

If you go down the list, you see normalization of albumin, normalization of prothrombin time. This is just a delight, you know, to look at this data, because there are very few instances that we have this kind of response.

So, although they don't have liver biopsies obviously because these patients are very fragile, that nobody is going to biopsy them at that point, although they may not have 100 percent negative DNA, these are remarkable data for decompensated liver disease, and this is one of the basis of my conclusions, that my personal conclusion is that adefovir looks excellent in these kind of patients.

DR. GULICK: Dr. Hollinger.

DR. HOLLINGER: Dr. Gulick, I won't be here tomorrow to discuss some of the questions about histology, but I thought since Zach Goodman is here, I would like to ask him a question about the fibrosis, because I think this is such a key issue, Zach.

What is difficult for me to understand is if you look at Poinard's data with hepatitis C and

some of the others looking at B and C, as well, we know it takes decades to get to cirrhosis, 30, 40 years for C, perhaps only 35 percent could reach cirrhosis in maybe 30 years or so.

So, what is difficult for me to understand is how, in 48 weeks, one can see a change in the Ishak's staging system from 1 to 6, of at least 1, and it just says equal to or greater than 1. I don't know what that mean. Does that mean 2, 3? I don't know what the median is on that score.

But it just seems an inordinate change in one year of the fibrosis score. I can understand the inflammatory score, it is not a problem, but the fibrosis score, I have a real hard problem with in terms of trying to determine this rapid change in 48 weeks, and maybe you could sort of give us some understanding of this basis.

DR. GOODMAN: I am sorry, I missed the last couple of words there. The question is how much change can you expect in a year. Part of it depends on how much you have to start with. Let's see, we have one for fibrosis, don't we? You are going to come up with a slide, okay.

I think there is lots of lines of data, of information, that are gradually evolving, that if

you can stop the process, whatever it is, inflammatory process or if we are talking about viral hepatitis--well, that's not it either. I don't think I need a slide--if you can stop the process, whatever the disease process is, then, things start to revert to normal, scars remodel. If you don't need it, you lose it. It happens in everything.

It was shown years ago in hemochromatosis, if you can deplete the liver of iron and then do a liver biopsy, a lot of times when there was cirrhosis there before, it doesn't look like cirrhosis anymore. Probably that is because the micronodules grow into macronodules, the scars remodel.

If you look at the absolute collagen content, it decreases. The same is true of Indian childhood cirrhosis in children. The children in India, this is a disease that doesn't exist much anymore, but it was due to copper overload. You deplete the children of copper and then do a liver biopsy a few years later, it doesn't look like they have cirrhosis anymore.

With hepatitis C now, we have effective therapy that actually eradicates the virus in many

patients. You do a liver biopsy in a year. They start to get better. Even if it's less than one point within any of the scoring systems, you can look at the two biopsies together and see that the fibrosis is resolving. Some of them who actually had cirrhosis at first, you see another biopsy, it doesn't look like cirrhosis anymore.

Now, maybe if we had the whole liver, we would still see some big nodules, but they are going away. I think the same must be true with hepatitis B. Within the context of a year, well, a lot of these people didn't have cirrhosis, they had a lot of portal fibrosis, but if you look at them side by side, you can see it is getting better. I think that demonstrates what the process is going through.

The patients who tell you about how much better they feel, well, why do they feel that way? It is not just the inflammation that is going away, their fibrosis is going away. Why does the patient who has ascites that is constantly being tapped have it going away? Well, the fibrosis must be going away, but we don't have serial biopsies to demonstrate that, because people won't put up with that.

We don't have long-term natural history studies with serial biopsies because our concepts of the diseases have changed over the years, and you just don't do it to people. You can't biopsy them every year to see how their disease is progressing.

Does that answer your question?

DR. GULICK: Mr. Grodeck.

MR. GRODECK: I would just like to comment on has the applicant demonstrated efficacy of adefovir among HIV and HBV coinfected patients. I think that is based on Study 460i, if I am correct--if I am incorrect, please let me know--I think tenofovir was excluded from study, in that particular study. So, therefore, I don't see the efficacy as being established in patients with tenofovir, and I think it's an important issue given the recent approval and widespread use of tenofovir in the coinfected population.

DR. GULICK: Just to clarify your point, you mean the study that we were shown, because it excluded tenofovir, you are looking for data which would have adefovir and tenofovir used together?

MR. GRODECK: That is correct. I actually saw a slide earlier that showed antagonism and

synergy between tenofovir and adefovir, and I just would be more comfortable hearing a little more elucidation on those two particular drugs in the HIV-HBV coinfected population.

DR. GULICK: Could we ask the sponsor, is there any clinical data available for people taking adefovir and tenofovir together?

DR. BROSGART: Just to clarify, the slide that was shown, that slide that was shown showed that tenofovir and adefovir are additive, there was antagonism, and it wasn't synergistic, but they clearly were additive. They have not been studied together in combination for the treatment of hepatitis B.

They are going to be compared prospectively, and that study has already begun. That is ACTG-5127, a study of patients with lamivudine-resistant hepatitis B failing therapy, who are going to be randomized to either adefovir 10 mg or to tenofovir 300 mg.

But what we do know is that from the in vitro data, adefovir and tenofovir are both active against wild-type HBV. They are both active against lamivudine-resistant HBV, and the in vitro activity is similar.

What we have in terms of in vivo data is obviously a very large clinical development program, over 2,000 patients, in the adefovir for HBV program. We do have a small amount of data on tenofovir in coinfection.

MR. GRODECK: What does that data show?

DR. BROSGART: What that data shows is that the antiviral efficacy observed at either 24 weeks or 48 weeks is similar to that seen with adefovir.

DR. GULICK: Carol, so there is no clinical data right now, clinical data on taking both drugs together, none available?

DR. BROSGART: There isn't. We are doing a drug interaction study this fall looking at the combination of tenofovir and adefovir. That is where we are beginning with that. What we do have is the prospective comparative data of tenofovir as compared to adefovir.

Then, after we have the drug interaction data, we can then decide whether to move forward looking at combination.

DR. GULICK: Thanks.

Other comments about the population with HIV-HBV coinfection? Dr. Schapiro.

DR. SCHAPIRO: Specifically to that issue, I don't think we have a large enough sample or I think the French data that was mentioned, we don't know about HBV/HIV coinfection. I think we also don't know the effect of this low exposure adefovir on HIV resistance.

We know that at high doses, adefovir does produce what we call classic tams or nams, the AZT mutations that were mentioned. I think there is a paper from Julie Sherrington from '98, and we know that that is a possibility.

The French study was small and I think at this point it is fair to say we don't know, so I don't think we have proved efficacy there, and I think we have to be cautious regarding the potential for HIV mutations to develop if the patient is being treated with the low dose of adefovir.

DR. GULICK: Dr. Wood.

DR. WOOD: I would echo Jonathan's comments precisely, and the only other issue regarding efficacy and safety in the coinfected population, given the small number, there are a substantial number of HIV-HBV coinfected patients who are going to be on other nephrotoxic drugs

chronically, such as acyclovir, and so forth. So, I would really like to see much more significant efficacy and safety data specifically in that coinfected population. I think 35 patients is just too small, particularly also given the resistance issues.

DR. GULICK: Dr. Englund.

DR. ENGLUND: I would like to even go further because I don't think there is--I haven't seen any good efficacy data for the HIV-infected patient at the 10 mg dose in substantial numbers, and I think that it should be part of the product's indication labeling, which we have some input in, that patients should be tested for HIV prior to initiation of therapy, as has been suggested for the use of lamivudine also I believe, at least it was discussed.

DR. GULICK: We are going to get back to labeling things. We might get back to that point.

Dr. London.

DR. LONDON: The point of efficacy against presumed precore mutants, I think there is a difference between having a precore mutant and not having a precore mutant, and I don't think that just because somebody is e-antigen-negative that

you can know that they have a precore mutation.

So, my question to the company is, do they have any data on actually documented patients who have precore mutations and have been treated.

DR. BROSGART: The Study 438 was done in the e-antigen-negative, e-antibody positive HBV DNA positive population. It was conducted in countries and regions of the world where precore mutant disease is very prevalent.

These were patients who were known to be precore mutant by their physicians for many years. We did a Phase II study where we enrolled patients with the exact same entry criteria, e-antigen-negative, e-antibody positive, HBV DNA at the same levels for this study, high ALT, and we did genotype those patients and confirm that in all of the patients in that study, they were precore mutants. They had the appropriate stop code mutations.

There was 100 percent correlation with our clinical definition. Given that we conducted the e-antigen- negative study only in areas of the world where precore mutant disease is highly prevalent and that these were patients who have been followed for years by their physicians for

their precore mutant disease and entered according to these entry criteria, we are confident that if we went and did the genotyping, it would show that there was these stop codence.

We did do genotyping, though, we genotyped all of the patients for A through G, and the patients in the e-antigen-negative study are in the appropriate genotypic classifications that correlates with patients who have precore mutant disease.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: Thanks. I just wanted to run through some of these specific questions and make a few additional comments.

To the overall question about efficacy in patients with compensated liver disease, I think that the sponsor has been quite convincing and that the paired liver biopsy data is a very strong endpoint in terms of determining that efficacy. I am very, very supportive of that indication.

I think the decompensated liver disease, this is a potentially life-saving drug, however, I have one concern in this area, and that is that patients seen in the community and are given a drug that is easy to take, are given that drug without

proper referral to a liver transplantation center, and I think that most of the hepatologists here would agree that all too often we see these patients very late, months after they decompensate and the patients become very cachectic and wasted, and have other conditions superimposed including worsening renal function with or without adefovir, and that we need to somehow emphasize that one must use caution and make proper referral for patients with decompensated disease.

This is an important drug. It is not the magic bullet, and it is not going to turn around every patient who has late-stage disease.

I think that the data on precore mutation is also very good, and the key issue that is raised here is that our typical markers of active infection, e-antigen positivity, are not going to be present, and that is going to increase significantly the importance of pretreatment liver biopsy and proper interpretation of those liver biopsies.

That is also something that has not been yet embraced at large by the non-hepatology community who treat these patients, and will become even more important as those patients are

recognized and a decision is made to treat them.

On the issue of coinfection with HBV/HIV, there is data. There is actually some prolonged data from Benhamou that looks at these patients, and perhaps the most important and encouraging thing in that group of patients has been the lack of emergence of resistance to date.

That said, the data are probably not sufficient yet for specific indication in the coinfected patient because we don't have a good understanding yet of interactions with other drugs, as well as the question of the emergence of resistance.

DR. GULICK: Other comments from the committee on any of the particular subgroups? I think we have touched on them all, but if anyone has anything to add about any of the subgroups? Dr. Sjogren.

DR. SJOGREN: There is one group that I keep forgetting, and those are the cirrhotics. I know Gilead showed us that they had 6, 9 percent of cirrhotics in each group, and they didn't explain to use what was the response rate in those particular groups. I think it is kind of important for us to understand, so we can recommend or not

recommend the product for cirrhotics.

DR. GULICK: Dr. Brosgart, do you want to respond to that, what is the response rate in the small number of cirrhotics that you all studied?

DR. BROSGART: We have three sources of information for cirrhotics. One are the patients who had cirrhosis in the pivotal trials, and improvement was demonstrated in those patients. I can show you that right now.

[Slide.]

So, this looks at regression from bridging fibrosis or cirrhosis. These are the patients who on the Knodell scoring for their fibrosis score, had a score of 3 or 4, and shows you who goes to a score of 1 or zero.

On the lefthand side is the e-antigen positive- patients, and on the right, are the e-antigen-negative patients. Thirty-nine percent of the adefovir 10 mg patients regressed from a score of 3 or 4, so bridging fibrosis or cirrhosis to a score of zero or 1 compared to 22 percent in the placebo patients.

Then, when we look in the e-antigen-negative, again, 34 percent of the adefovir 10 mg compared to 22 percent on the

placebo patients. But our other sources for data on patients with cirrhosis actually do come from the transplantation study.

This was the data that Dr. Sjogren was referring to, and we showed you the baseline characteristics for the patients who were either in the transplantation group or the patients wait-listed for transplantation, and the high proportion who had CPT scores greater or equal to 7, which some of you may know as a Child V or a Child C, those are cirrhotics, and along with that, they had evidence of decompensated disease. Those were the clinical markers that we showed you improved when they were treated.

The last area where we have data comes from a study we have done with GlaxoSmithKline, Study 465. It was discussed in the Backgrounder. It was an open-label study in 40 cirrhotics who had lamivudine-resistant HBV.

They were treated with open-label adefovir added to ongoing lamivudine. Those patients have had HBV DNA reduction. Their HBV DNA has gone to undetectable. Their clinical parameters have improved, their Child-Pugh scores have improved, and that data was presented by Bob Perillo, the

24-week data, at the American Association for the Study of Liver Disease last November. At the follow-up, the year-long data will be presented at the next meeting in November.

DR. GULICK: Thanks. Can I ask you what the sample sizes are on this slide?

DR. BROSGART: The n's for that, well, for cirrhosis, was 6 percent and 11 percent in one study.

DR. GULICK: You mean of the total sample?

DR. BROSGART: Right. I can come up with the n's in a few minutes for you. We have them here.

DR. GULICK: That will be great.

Let me summarize a little bit about what we have said about effectiveness and then again, we are going to take a formal vote.

I think it was the consensus of the committee that effectiveness was seen with adefovir for chronic HBV with the primary endpoint of histology. People noted improvements in both inflammation and fibrosis were particularly notable, also multiple second endpoints including HBV DNA, ALT, e-antigen conversion, and then in the decompensated group, Pugh score and laboratory

tests of liver function like albumin and prothrombin time.

Some members of the committee commented it is particularly notable of the effectiveness in certain subgroups like the decompensated group and those with lamivudine resistance. Others noted the differences between adefovir and the other agents available for the treatment of this disease, in particular, interferon and lamivudine.

A question came up about how well these markers correlate with clinical benefits. Dr. Sherman reviewed some of the data, extrapolating from hep-C and then making the point that changes in anatomy are likely to lead to changes in clinical endpoints.

Several people mentioned the 48-week limitations of what we have once again, pointing out the analogy to the lamivudine approval, which was also based on 48 weeks of data, and the problems with resistance that came out after that approvability.

Several people made the comment about the generalizability of these results to the hepatitis B population at large, and commented that this was going to be a challenge to education as to who to

treat for hepatitis B.

On one other point about effectiveness made by Dr. Mathews, was clearly the effectiveness of 10 mg of adefovir was less than 30 mg overall, so some question of potency even with all the other endpoints in mind.

Regarding the specific subpopulations, people felt that there was strong data to support benefits in the compensated disease group. We heard a difference of opinion in the decompensated disease group. Dr. Sjogren used the word "remarkable." Dr. Sherman talked about potentially life-saving. Dr. Wong pointed out to us that this was uncontrolled data based on HBV DNA endpoints as opposed to histology in this group, and then we just heard some data on cirrhotics, which would also be part of that group.

People felt that this data was very strong in people with lamivudine resistance and also very strong in those with presumed precore mutant, although as Dr. London pointed out, there was some uncertainty about the presence of the mutations.

Finally HIV coinfection, I guess most of us felt that there was not enough data to really make conclusive statements about the effectiveness

of adefovir in this group. We noted that the one study quoted had a sample size of only 35, that there were no controls in that group.

There were some concerns specific to the HIV-coinfected patients, such as the fact that this may select out resistance mutations in HIV, particularly at its low dose. The potential for using other nephrotoxins and then pharmacokinetic interactions with other drugs that HIV-infected patients use.

Dr. Stanley reminded us that resistance is a part of effectiveness, and Dr. Schapiro and Dr. Stanley noted that we have information for 48 weeks, but that that is probably not enough, that it is good to see that there weren't mutations there, but that is not the same thing as saying that there never will be and that the long-term resistance is really unknown, that there is more that can be done and better techniques could be used.

Let's take another vote here. We will go that way this time.

DR. FLETCHER: I have got a clarification.

DR. GULICK: Oh, a clarifying last-minute important comment.

DR. FLETCHER: Well, just now, if we are preparing to vote on Question 2, I agree with Dr. Wong's assessment of effectiveness where it was demonstrated and where it wasn't. If you read Question 2 as it is, it says has it demonstrated effectiveness for the treatment of chronic hepatitis B. To that broad question, I am not sure the answer is yes. To some subsets of that question, particularly to compensated, I think the answer is yes.

I, at least, need to hear are we really going to vote on this as it is worded. I mean if the pivotal studies, you know, 437 and 438, only included patients with compensated liver disease, so now if we begin to talk about an indication, are we really prepared to go beyond the types of patients the two pivotal studies enrolled.

DR. GULICK: Let me again ask the agency for some guidance on this question. I think we are having the same issue we had with safety.

DR. GOLDBERGER: We expect the members of the committee obviously to consider all the issues. We put up a sampling of some of the ones that we are particularly interested in, and some of the reasons we are interested in them reflect the fact

that we have to deal with some of these issues in the writing of labeling, in thinking what particularly a clinical study section might look like, in thinking about issues for Phase IV studies, and about further development of the product.

From the point of view of committee members, we expect the committee members to take into account the types of issues that have been discussed, and to make judgments overall within their own mind broadly about the issue of, for instance, in the case of Question No. 2, the effectiveness.

We do specifically ask if people have caveats or concerns, to express them for the reasons I outlined a few moments ago, because those are very important to us in a variety of processes both before and after approval, but one of the reasons we look for people with a broad range of expertise is because of our expectation that you will be able to do this calculus and come up, frankly, with a broad answer or do as good a job as you are able.

So, we want you to give a broad answer to the question. If there is a specific caveat, just

as in the safety question, some people brought up the issue of 48 weeks, feel free to do that because that information is useful to us as we go about some of our other activities.

DR. GULICK: I knew he was going to say that actually.

DR. FLETCHER: May I have a question?

MR. GRODECK: Yes, Dr. Fletcher would like to push you.

DR. FLETCHER: In the labeling, if we get to that point, would the agency consider a label that says, you know, adefovir is indicated for the treatment of chronic hepatitis B in patients with compensated liver disease?

DR. GOLDBERGER: What will happen is that after the meeting, we will go back, everyone here internally will talk about what they have heard at the meeting, and we will talk with the company, et cetera, about their perspective and what they have heard. If necessary, we will go back and look at certain parts of the data that were submitted in the NDA, and try to come to a conclusion, for instance, if a statement, an unqualified statement as an indication is appropriate, if a qualified statement as you have outlined is appropriate, if a

statement that simply says that, you know, there is limited data in such and such a group, or whether we choose to deal with this, for instance, by including extra information in the clinical study section, those are some of the options that we have available.

It would be a little premature now to tell you what we would absolutely do, but in the past, we have used all those approaches in dealing with problems like this.

DR. GULICK: So, again, from our point of view, at previous meetings, at times we have considered a restricted indication versus a broad indication. Is that something that you want us to do today?

DR. GOLDBERGER: Well, I think it would be helpful if committee members feel strongly that there are clear caveats, and actually, I think if you were to look, for instance, at Question No. 4, I think Question No. 4 talked a little bit about extra information about safety and effectiveness that we thought needed to be included in the labeling.

That is probably a place if you want to bring up some of these issues, you know, please

feel free to do it for the reasons that I outlined before. We find this advice from the committee to be extremely useful in interacting with the company and in forward planning.

DR. GULICK: Okay. So, let me pose again the question to the committee. We have all heard the instructions, so if people have restrictions or caveats they would like to make to their vote, that is appropriate to do.

So, has the applicant demonstrated the effectiveness of adefovir 10 mg daily dose for the treatment of chronic hepatitis B?

We are going to start with Dr. Wong this time.

DR. WONG: Yes, and I will express the caveat that they have demonstrated it insofar as the study population is defined for the pivotal studies, and they have not demonstrated it in the supplementary groups for which there were no controls.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: I will say yes, but I would be of the opinion that there should not be any restriction to people with compensated liver disease, that the label should simply add a

description of the clinical studies, because the people most in need are the ones with decompensated liver disease. The last thing I would want to see happen is that there would be barriers put up in terms of their access.

DR. GULICK: Dr Sjogren.

DR. SJOGREN: My answer is yes, and the only group that I hesitate, and I would like a caveat, is the HIV-HIV coinfection.

DR. GULICK: Dr. Hollinger.

DR. HOLLINGER: Yes.

DR. GULICK: Dr. DeGruttola.

DR. DeGRUTTOLA: Yes with the caveat of Brian Wong.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: The same, yes to the caveat of Dr. Wong.

DR. GULICK: Dr. Stanley.

DR. STANLEY: Yes until that resistance develops.

[Laughter.]

DR. GULICK: Dr. Englund.

DR. ENGLUND: Yes with the exception of the HIV coinfection.

DR. GULICK: Dr. London.

DR. LONDON: Yes, and I agree with Dr. Mathews that the decompensated patients may be the most in need and the ones who would benefit the most.

DR. GULICK: Dr. So.

DR. SO: Yes.

DR. GULICK: Dr. Schapiro.

DR. SCHAPIRO: Yes.

DR. GULICK: Dr. Kumar.

DR. KUMAR: Yes with the exception of coinfection with HIV.

DR. GULICK: Dr. Kopp.

DR. KOPP: Yes.

DR. GULICK: And Dr. Wood.

DR. WOOD: Yes with the caveat of the HIV coinfected group.

DR. GULICK: And the Chair votes yes with the caveat about HIV infection also.

DR. GOLDBERGER: You can see, Mr. Chairman, that, in fact, it is not that painful to actually have the vote.

[Laughter.]

DR. GULICK: I would say pain is in the eye of the beholder.

[Laughter.]

DR. GULICK: Let's move to the third question.

Based on the risk-benefit profile, does the committee recommend approval of adefovir 10 mg daily dose for the treatment of chronic hepatitis B in adults?

This time, the discussion is really open to how you weigh the first two questions, the safety information with the effectiveness information, how do you weigh those two, and eventually, we will take a vote about formal approval from the committee.

Do people have any comments about weighing risks and benefits? This may be relatively short.

Dr. Wood.

DR. WOOD: I think the issue is, is that the benefits regarding specific surrogate markers are known through certain time points of the study in terms of histopath benefit, HBV DNA benefit, seroconversion.

The risks, unfortunately, for many of the things that committee members have previously raised, are unknown for certain parameters, specifically prolonged duration of treatment and adefovir exposure beyond 48 weeks regarding

nephrotoxicity, that is unknown. The issue of resistance with chronic exposure, that is unknown.

So, I just put that out as a general out there about the risk-benefit, because the benefits, I think we have are clearly documented. Our greater struggle is with the unknown risks that we have given how the drug is like to be used or need to be used.

DR. GULICK: Thanks. That is well said.

Mr. Grodeck.

MR. GRODECK: I would just like to comment on do the risks include going off the drug, and if that is consideration, if it is taken indefinitely, there is a different requirement. If it is two years until some sort of kidney abnormality develops and then you are forced to go off drug, I think there are more risks. It is just something to consider.

DR. GULICK: Thanks.

Other comments about risks and benefits here?

Okay. This is an easy one to sum up, because I think Dr. Wood did it, or as Dr. Wong pointed out, we have already discussed safety and efficacy in our own minds. We are weighing these

against one another.

The biggest uncertainties we have is simply data that we don't have. After 48 weeks, what is the incidence of resistance, and then as was just said, what are the risks of discontinuation of the drug. So, we are plagued by data we don't know yet. We feel we can evaluate the risk-benefit ratio with the data we have.

So, let's take formal vote again. Again, this is to recommend approval of adefovir 10 mg for chronic hepatitis B infection.

Dr. Wood, we will start with you.

DR. WOOD: Yes.

DR. GULICK: Dr. Kopp.

DR. KOPP: Yes.

DR. GULICK: Dr. Kumar.

DR. KUMAR: Yes.

DR. GULICK: Dr. Schapiro?

DR. SCHAPIRO: Yes.

DR. GULICK: Dr. So.

DR. SO: Yes.

DR. GULICK: Dr. London.

DR. LONDON: Yes.

DR. GULICK: Dr. Englund.

DR. ENGLUND: Yes.

DR. GULICK: Dr. Stanley.
DR. STANLEY: Yes.
DR. GULICK: Dr. Fletcher.
DR. FLETCHER: Yes.
DR. GULICK: Dr. DeGruttola.
DR. DeGRUTTOLA: Yes.
DR. GULICK: Dr. Hollinger.
DR. HOLLINGER: What would a no sound like? Yes.
DR. GULICK: Dr. Sjogren.
DR. SJOGREN: Yes.
DR. GULICK: Dr. Mathews.
DR. MATHEWS: Yes.
DR. GULICK: Dr. Wong.
DR. WONG: Yes.
DR. GULICK: And the Chair votes yes.
That is unanimous, 15 yes, zero no. That is what that sounds like.
It is 20 of 5:00. Let's just take a deep breath here instead of a break.
As Dr. Goldberger instructed us, perhaps a lot of the important information we can help is by discussing the next question, which is: Are there issues with the safety and effectiveness data that should be highlighted in the drug label? In

particular, please discuss the use of adefovir in HIV coinfection and the risk of NRTI resistance. In addition, safety and efficacy monitoring issues will probably come up here.

Dr. Schapiro.

DR. SCHAPIRO: I think some issues that have to be in the label to communicate to the clinician. One is that the issue of resistance is unclear. I think that has to be adjusted somewhat from what we heard in the briefing. We heard comments, but I think that is very important that it should be clear that we don't know.

I think regarding HIV/HBV coinfection, not only the lack of data regarding that patient subpopulation, but it is important that clinicians be aware that we haven't yet really evaluated the risk, and these are not only 65 and 70, but specifically, AZT mutations develop in these patients.

Just to touch on I think two other points that were mentioned, one is the risk of stopping therapy and guidance, the fact that we don't have a good handle on that, and I would also just one more time mention the fact that the study was done for 48 weeks does not imply that that is the

recommendation for therapy.

Somehow that has to be--I think that was the flavor that came out here--I think that has to be very clear to the clinician in the label who didn't hear this whole discussion.

DR. GULICK: Dr. Kumar.

DR. KUMAR: I want to echo the last part of what Dr. Schapiro said, that somehow in the label we need to indicate that we really do not know how long to give this drug to patients with chronic hepatitis B infection.

DR. GULICK: Dr. London.

DR. LONDON: I am concerned that clinicians out in the countryside or country are going to misinterpret the 48-week duration of information. We actually have information that when the drug is stopped, there is a good possibility of a flare, and I think that somehow that has to be conveyed because what has happened with lamivudine is that it is just sort of a practice now in the community, treat for a year, stop.

I think if you treat for a year and stop with this drug, and really get 25 percent of the patients developing these major elevations of ALT,

you will soon see a big paper in the New England Journal of Medicine, and it will kill the drug.

So, I think that we have to warn the community of doctors that discontinuing the drug carries a risk of a flare of hepatitis, and I think it should be in the drug label.

DR. GULICK: Dr. So.

DR. SO: I think clearly we have to address the issue of potential nephrotoxicity and also the monitoring where there is every three months BUN creatinine, and also the risks of taking other drugs with known potential nephrotoxicity and the known interaction between adefovir with these other nephrotoxic drugs.

DR. GULICK: Dr. Kopp.

DR. KOPP: To follow up on that, I would propose that a baseline GFR be estimated by creatinine clearance or MDRD equation, and for GFRs less than 50, therapy not be recommended pending the results of the 536 study, available I guess in about 18 months.

DR. GULICK: Other comments on that? Dr. Wong, you brought that point up before.

DR. WONG: I don't know if I would agree with that. I would not try to restrict this drug

to people who have normal renal function, but I think that physicians need to be warned that there really is very little safety data available in those patients, so they are going to have to be very careful, but I don't think I would try to tell people that they should not treat their patients who need treatment just because their GFRs are below 50.

DR. GULICK: Dr. Sjogren.

DR. SJOGREN: I think in the label it should be specified what type of patients with chronic hepatitis B should be treated, and among them, people with, like we have said, compensated liver disease, that have demonstrated liver disease in liver biopsy. Also, to point out that this drug is effective in cirrhotic patients and perhaps with some kind of limitations because of the lack of the control group, but still very good and effective in decompensated liver disease. I think that message needs to perhaps be qualified in some way, because, you know, there are not a sizable number. There were controlled studies in some of them, but it is still important for the clinicians to know.

DR. GULICK: Dr. Stanley.

DR. STANLEY: I think as far as the

nephrotoxicity, we need to put in the label that it is unknown whether that can be a cumulative risk for physicians to be aware of, and then as far as the issue of whether a liver biopsy should be done and how frequently, I would ask our liver experts to weigh in on that.

DR. GULICK: Liver experts want to weigh in on that?

DR. HOLLINGER: We can do this since we are on the panel here, this is your show here, but the question is there are some consultants here who have been involved with this. It might be interesting to just get a quick answer from those three or four over there about what they think about the biopsies before and after. Would that out of line, Dr. Gulick?

DR. GULICK: No, sure.

DR. HOLLINGER: You have got Dr. Wright, Dr. Dienstag, Schiff, and there are others, too.

DR. GULICK: The small God.

[Laughter.]

DR. GULICK: So, the specific question that we are looking to our colleagues to answer is would you require a biopsy or even recommend a biopsy.

DR. WRIGHT: Teresa Wright, San Francisco.

I think we, as hepatologists, with hepatitis B, as with hepatitis C, are still using the liver biopsy to guide to as the urgency of treatment in diseases where there are still unknowns about long-term safety and efficacy, treatment stopping, much of what we have discussed.

I think we still would err on the side--we would advocate treatment for patients who have significant fibrosis and might be a little bit more inclined to continue to watch individuals who have very, very mild liver disease.

That is my personal opinion.

DR. SCHIFF: I am Gene Schiff. I am from the University of Miami.

I would agree with Terrie, but I would never be dogmatic about it, that you must have a liver biopsy in every patient. It is preferable that you do in the beginning, so that you can establish the histologic severity, but I would not make it mandatory.

DR. DIENSTAG: Jules Dienstag, consultant, I guess.

I think that most of us who are hepatologists, before we apply a therapy that would

be used long term, like to get a baseline biopsy. Without a baseline biopsy, if we ever need another biopsy at any other time to evaluate what is happening to our patients, for example, if there is a flare later or resistance later, without that baseline biopsy, we really can't interpret a later biopsy.

So, in addition to what Gene and Terrie said, I think that is another important reason to do baseline biopsies.

Ultimately, I suspect, the scale of therapy, given the number of people who have this disease, will force the therapy of this disease into the hands of people besides hepatologists. Now, we, as hepatologists, have a vested interest in keeping this type of therapy amongst ourselves, but ultimately, when infectious disease people and internal medicine physicians start treating, there probably will be some shift towards using fewer biopsies, but from the hepatologist's point of view, there are very, very good indications, very strong reasons for using, for relying on biopsies.

DR. GULICK: Thanks.

Other issues to discuss? Dr. Wong.

DR. WONG: Just at this point, without a

liver biopsy, it seems to me there is no way for a physician to know that is patient, his or her patient is comparable to the patients who are treated in this trial, so that it would be pretty difficult to recommend giving treatment like this with an open-ended time commitment without that information.

DR. GULICK: Dr. So.

DR. SO: There is another line of thought. You know, I think a lot of physicians out there are treating chronic hep-B if they have replicative disease at the levels, just like what Gilead used over 2 times above the upper limit of normal for ALT, and they would be patients who are considered suitable.

DR. WONG: [Off mike.]

DR. GULICK: We are back. Thank you.

Dr. Wong, did you have something else to add?

DR. WONG: I just said that one would like to know before treating a patient, that the patient is roughly comparable to the patients in whom the efficacy of this treatment was demonstrated.

DR. GULICK: Is it safe to say that the consensus of what we heard is that people would

strongly recommend, but not require, was that consensus I heard?

DR. SO: Actually, I disagree because there is a population, you know, especially patients with decompensated liver disease, if you do a biopsy with a low platelet count, portal hypertension, they are very high risk for a major complication of bleeding.

Occasionally, people die from liver biopsies, so really, from a patient advocacy point of view, I don't think it is absolutely necessary unless you are doing a study like this, because how many of these patients actually get re-biopsied after a period of treatment and whether the re-biopsy actually determine cessation of treatment.

Once again, these are issues. I hope tomorrow you folks will address.

DR. GULICK: Right. I think that is going to be a big topic for tomorrow.

Dr. Hollinger.

DR. HOLLINGER: In essence, though, but to answer the question, no one is going to biopsy somebody who you already know has cirrhosis, and any first-year medical student can maybe make that

diagnosis on somebody like this.

I think what one is talking about is biopsying somebody else, somebody that has got a coagulopathy, a low albumin, and ascites, or other things, no one needs to biopsy that patient to know that they have got cirrhosis.

So, I think really the issue is biopsying that other, very large group, where you are really not sure how much fibrosis or liver disease there is. In those cases, even though you say it certainly would be not required, I think the emphasis for most of us would be that a biopsy really is essential in the baseline, and it is only the rare circumstances, as maybe Gene Schiff has said, that you might get by with not doing it.

DR. SO: But is that treating the physician or treating the patient, because are you basing that information to determine whether you are going to not start treatment? If the ALT is--you know, if the patient has a very high viral count, okay, and the ALT is three or four times above normal, are you actually saying that in the biopsy, which it could a sampling error, well, you don't get a lot of information, you base it on that rather than the other information, not to start

treatment? I don't know.

DR. GULICK: What I am hearing is that we shouldn't be dogmatic about this, and obviously, we can't go into every case about the pros and cons of liver biopsy, but that, in general, we should strongly recommend, but not require this for patients. That is what I heard.

Dr. Schapiro, I didn't hear that?

DR. SCHAPIRO: Well, I am not clear. Again, going back to hepatologists, in light of this drug, and we are talking about this drug, I don't see how a biopsy is going to guide our decision to start or to stop therapy. I am trying to think how many of these patients, given again the clinical criteria, how many of these would have been changed by the first biopsy, and would I stop treatment based on any results of the second biopsy. Maybe sometimes, but why would it be strongly required in light of what we saw here for this drug?

DR. WONG: What if the histology is normal, I mean would you treat that patient immediately? We have seen evidence of risk here, right? So, if you don't see any histologic abnormality, it would seem to me that that is a

patient who could be followed since we know we are exposing the patient to nephrotoxicity, development of resistance, flare, all these things, right?

DR. SCHAPIRO: Maybe we can ask for hepatitis B based on these clinical criteria, what percent of patients would be normal.

DR. GULICK: Dr. Sjogren, can you help us?

DR. SJOGREN: The way I look at this, the biopsy is going to help us start or not start the therapy. It is not going to help us stop, but start the therapy, and so we select the patient that needs the therapy and that we can take the challenge of 48 weeks, 96 weeks, 110 weeks, however long that patient may or may not have to stay, because we see evidence of severe liver disease.

So, it is not much into the future, but at the present time, am I putting a patient at risk, at unnecessary risk because he has minimal disease or no disease. That is the question that I think we are attempting to answer, so decide whether that patient goes on therapy or not. I think that is an important criteria.

Obviously, there are patients that we cannot do the liver biopsy, and the exception makes the rule, and so I agree that we shouldn't have an

automatic 100 percent or nothing, but I think it is more than recommended. I would consider more, maybe "require" is not the word either, but there must be something in the wording.

DR. GULICK: Strongly recommended.

DR. SJOGREN: Strongly recommended because of the unknowns. I think as we develop experience with drugs, as we know now interferon, as we know lamivudine, we may tend to change, and four years from now we may be saying, hey, adefovir, no more biopsies, you know, it is a great drug blah-blah-blah. But that is not where we are now.

We are in the presence of a new drug that has potential toxicity, and I think we need to be careful in how we select our patients or else we could ruin the drug, and we can ruin our patients, as well.

DR. GULICK: Let me again just observe that we are going to talk about this a lot tomorrow, so we may want to curb the conversation.

Dr. Mathews.

DR. MATHEWS: Could I ask, does the lamivudine label say anything about liver biopsy before starting therapy?

DR. BROSGART: I don't think that there is

information or wording in the lamivudine label.

DR. GULICK: We can't hear you. The answer is no?

DR. MATHEWS: Another way to deal with this is just--I mean that is what practice guidelines are for, I think, I am not sure it needs to be in the label.

I would also point out that there are probably thousands of people with HIV who have been unintentionally treated for hepatitis B as part of their HIV therapy, and very few of those people are referred for liver biopsy unless they have significant transaminase elevation or signs of active liver disease.

DR. NGUYEN: Could I just make a comment?

DR. GULICK: Yes.

DR. NGUYEN: There is no medical officer who is in doing the 3TC, but I believe the last time I reviewed the label for 3TC for hepatitis B, I think it was indicated for chronic hep-B with evidence of active viral replication and active disease, I believe. Is that true for Gilead folks?

GILEAD: [Nodding.]

DR. NGUYEN: They mentioned the fact they would have to have active viral disease and active

replication of virus.

DR. GULICK: Chris, someone just handed you the label?

DR. MATHEWS: Correct. It says, "Indicated for the treatment of chronic hepatitis B associated with hepatitis B viral replication and active liver inflammation. This indication is based on one-year histologic and serologic responses in adult patients with compensated chronic hepatitis B and more limited information from a study in pediatric patients."

DR. GULICK: Thanks.

DR. SJOGREN: We have to learn from our mistakes, you know, because I was a member of the panel, and we didn't know about resistance. We didn't know a whole lot of things of lamivudine back then as we know now, so we need to learn from our mistakes.

DR. GULICK: That seems like a good place to sum up. Dr. Englund.

DR. ENGLUND: I just had one other comment. I want to make sure. Sharilyn was saying that there wasn't--I want to make sure that it's acknowledged that there is some evidence of cumulative renal disease. I think that there was

some good evidence of the cumulative renal disease, not just the acute, but it accumulates, that there may have even been more at 96 weeks if you can read it, and that that absolutely needs to go in the labeling, that it is not just that there is renal disease associated, but it looks like it's progressively and it accumulates.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: I agree with Jan. That cumulative risk is in patients that had adequate renal function at baseline, so it is not just in patients that had some renal insufficiency, but patients that had normal function at baseline because I am sure the sponsor would be disappointed if I didn't say something about drug interactions.

I think, you know, the label does need to highlight some issues that I think in general, the drug interaction profile is not understood. It is not well understood or well characterized.

I have a general problem with the statement, for me, by saying there are no clinically relevant drug interactions. Drug interactions by their nature are almost never studied to be clinically relevant.

I mean you don't do the study, you do a

very short-term pharmacokinetic study, find out whether there is a change in levels, but to draw some inference from that in terms of whether it is clinically relevant or not, most of the time the data never exists to do that, so I would be very careful, in fact, would probably discourage that type of a statement.

A couple of points to that. Adefovir increases, you know, the concentrations of ddI. It is interesting that tenofovir does that, as well, so what is that mechanism with these two drugs and an increase in ddI concentrations, and I don't think we can be confident that that might not be clinically relevant.

The ibuprofen-adefovir interaction, I think is one that may need to be approached cautiously, as well. It's a 20-some percent increase in area under the curve, and I think there may need to be again some caution with saying that that would not be clinical relevant.

Lastly, with regard to the HBV/HIV coinfected patients, I think the situation with protease inhibitors, you know, the ACTG359 study both in its smaller, intensive pharmacokinetic study, as well as in the larger study that was

presented at the Retrovirus Conference this year, and shows an interaction between saguinavir and adefovir, and can we be confident that there aren't interactions with other protease inhibitors, and not interactions with the immunosuppressive drug cyclosporine, tacrolimus, so I am pleased that the sponsor has studies for those drug interactions planned.

Again, just as a final comment, the statement has been made here that adefovir is not a substrate, not an inhibitor of cytochrome p453A. I am just struck again by the Backgrounder from the company, at least on page 80 says that cytochrome p453A was inhibited by adefovir dipivoxil at concentrations of 19 and 83 micromolar.

I understand that those are very high concentrations, but at the local site, you know, perhaps there really may be interactions there.

So, I think just in terms of issues that need to be highlighted, just to sum up, I think the issue about clinically relevant drug interactions really needs to be rethought, you know, how to state that.

DR. GULICK: Dr. Birnkrant.

DR. BIRNKRANT: Before we move on to the

Phase IV commitments, which we have already begun to touch on, can we get some comments related to the adequacy of the dose modification scheme proposed for patients with renal insufficiency? I will clarify for you. Is it adequate to initiate dosing versus is it adequate to dose-modify in someone who is being chronically dosed?

DR. GULICK: Who would like to start? Dr. Kopp, can you help us here?

DR. KOPP: I am not sure I understood your last comment. Do you want to distinguish that, dose-modify for somebody who has developed renal insufficiency on the drug?

DR. BIRNKRANT: Right, is there adequate data to support that?

DR. KOPP: Well, I expressed my discomfort earlier with the proposals that we have got based on the area under the curves that we saw.

DR. BIRNKRANT: Do you feel comfortable, though, initiating therapy in patients with renal insufficiency based on the scheme put forward?

DR. KOPP: Again, we have three groups. We have people with normal renal function, yes, 437 and 438. It probably included people down to GFRs of 40, estimating a serum creatinine of 1.5 in a

woman, say, of age 40. So, those patients in general seemed to tolerate the full dose relatively well, and really, my discomfort is in patients with GFRs below 40 to 50.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: Another point, and that is that in the very sick patient, I assume that nomogram applies to people with stable but abnormal renal function, but many of these patients do not have stable renal function, so I wouldn't have any way of knowing how to dose it in a hospitalized patient in that setting.

DR. GULICK: Dr. Kopp, could you address that?

DR. KOPP: Yes, I was thinking about the same thing earlier. I think once you have a creatinine that reaches a peak and then begins to decline, that peaks defines what a new, nonchanging GFR is, but you are exactly right. If you admit a patient with a creatinine of 1.5, and the next day it is 2, you know the GFR is very low, but you don't know, is it 5, 10, 15, or 20, and there is really no nomogram to help you at that point.

I guess the safest thing from a renal perspective is to stop a renal toxin in a setting

while the creatinine is rising, and therefore, the GFR is falling until the situation has declared itself, and that might occur in a few days or a week, and hopefully, that is enough time that you won't get one of these flares of HBV that we have been hearing about.

Certainly, in clinical medicine, we all know that in some situations, you have to keep a renal toxin going even in the face of a rising creatinine, amphotericin, cyclosporine, or what have you, but it is always a moment-by-moment decision by the clinician about which is worse, not treating something or using a renal toxin, and in this setting, it is really no different from any other clinical decision that has to be made, the use of gentamicin in a septic patient with a rising creatinine, but a need for the therapy.

I am not sure we can provide too much guidance on this. I think ultimately, it has to be for the clinician at the bedside to decide.

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

DR. FLETCHER: I think as a place to start in patients that had baseline renal insufficiency, the nomogram, at least it seems to make some sense to me. If you think just in terms of half-life, if

a normal plasma half-life is about 7 hours, if someone has a 50 percent reduction in creatinine clearance, so it should be about 14 hours, and if you dose every 3 or so half-lifes, you know, then, a dosing interval of every 48 hours, you know, as you get down there, it makes some sense.

I clearly think the nomogram needs some clinical experience with it. The second point where I would begin to get more concerned is as you get less than 20 mL/minute, that is where these really begin to have some difficulties until they are tested. The computer simulations always look good, but until you really test them down there, you just don't know.

It was just pointed out. I think patients on therapy that develop renal insufficiency, serum creatinine is always going to lag behind, and so will creatinine clearance, and so you can always be somewhat chasing your tail a little bit.

So, again, I think some real experience with the nomogram in patients that have changes in renal function while they are on therapy is going to be critically important.

If I could just ask the sponsor on that one quick question, at least it would be helpful to

me to think--because I think in terms of half-lifes--in someone who has a creatinine clearance less than 10 mL/minute, what is the half-life, so that it would be that off-dialysis half-life?

DR. KEARNEY: Are you specifically asking in end-stage renal disease patients?

DR. FLETCHER: Right, exactly.

DR. KEARNEY: When we studied the end-stage renal disease patients when they are not receiving hemodialysis, there was no extra renal route of elimination observed, so the concentration time profile was completely flat, and no eliminate half-life could be determined.

DR. FLETCHER: Can you put a greater than to it, it has got to be greater than? You did your sampling out for how many hours?

DR. KEARNEY: We sampled out to 96 hours.

DR. FLETCHER: So, the half-life then, it is fair to say, has got to be greater than 96 hours in that end-stage renal disease patient?

DR. KEARNEY: Yes.

DR. GULICK: Dr. Wong.

DR. WONG: While you are up there, you showed us your computer model for the

pharmacokinetics in patients with varying renal function, but it was only up there very briefly. As I looked at it, it looked to me like your nomogram was predicated on the idea that you were going to try to make the troughs equivalent, is that correct?

DR. KEARNEY: Right. Adefovir is currently only available as a 10 mg tablet.

DR. WONG: Right. So, you have a choice of trying to make the troughs equivalent, making the peaks equivalent, or making the AUC equivalent, or some variation thereof, and you took the one or you chose to pick your nomogram parameters, having the effect of going for the highest dose of those three possibilities, it would seem to me.

I don't know that that is really what I would do. We have seen a lot of data over the years on the nephrotoxicity of this drug that really is unquestionable, and I might be a bit more conservative on the dose, perhaps trying to make the AUCs equivalent as opposed to the troughs equivalent.

DR. KEARNEY: I think that is critical additional work that needs to be done once an alternative dosing formulation is available.

DR. WONG: But what I mean in the absence of any data from your prospective trial that you are planning, you have to pick someplace to start. I guess if someone came and asked me where to start, I would probably be a bit more conservative than you have been.

DR. KEARNEY: In determining dosing guidelines with a fixed dose formulation, you are limited in terms of what you can do with Cmax and AUC. A fixed dose into a fixed volume will result in a Cmax that you can't really alter, so extending the dose interval allows us to target trough concentrations.

DR. WONG: I understand. I am not saying that you shouldn't extend the dose interval, but you can extend it from every one day to every two days, or from one day to every four days, or one day to every seven days, right? I mean you have a choice there, and it seemed to me that you picked an interval to make the troughs equivalent, which results in greater total drug exposure for the people with renal insufficiency than in those with normal renal function.

One doesn't have to choose to do it that way.

DR. KEARNEY: In our pharmacokinetic modeling, we tried to balance basically, we wanted to limit adefovir exposure as much as possible, and the trough concentrations in the moderately and severely impaired patients, in the moderately impaired patients, are about 50 percent lower than in unimpaired patients with 10 mg, and about 85 percent of those normal patients.

So, we lowered the trough as low as we felt comfortable, but we didn't want to go to the next day because this would provide a complete drug-free interval for patients.

DR. GULICK: We need to complete the discussion here. So, just the highlights of what we recommended for the drug label, appreciating that we have 48 weeks of data, and not more, and that that is both safety and durability data. Several people brought up the concern about what is the optimal duration of treatment.

In terms of what types of patients should be treated, we read aloud the lamivudine brochure. Certainly, people identified the ones in the pivotal study compensated with active liver disease.

We heard the discussion about biopsy

strongly recommended, but not required. Decompensated patients and cirrhosis, that there are more limited data, but also impressive results in terms of some of the endpoints. 3TC resistance again, patients with 3TC resistance showing strong responses.

We spent some time being concerned about the HIV coinfected patient given the limited data, the risks of resistance, con meds and drug-drug interactions. In terms of safety, we were most concerned about the renal toxicity. Several people made the point that there appears to be cumulative toxicity through 96 weeks, both in people with normal renal function at baseline and those with abnormal, but it remains an open question about how important that is going to be, but people should be made aware of it.

In terms of people with abnormal renal function, Dr. Kopp suggested getting a baseline GFR on people, and then there was some differences of opinion about treating people with baseline creatinine clearance less than 50.

Dr. Kopp was strong and suggested not recommended, others suggested a warning that these patients need to be closely followed.

We talked about the formal recommendations for dose interval reduction that Gilead has made including the latest conversation. Dr. Fletcher reminded us that this is based on pretty sound PK principles, but reminded us that we really don't have the clinical data yet to support those recommendations. As he said, it is a place to start.

Less clear is what to do with people who develop increased creatinine on the drug - should you stop, should you dose reduce, and what do you do in someone with changing renal function over time, and that is critically important to avoid toxicity.

Previous suggestion monitor creatinine Q 4 to 8 weeks, the committee was more comfortable with than 3 months, and again a warning about concomitant nephrotoxins.

Another area was resistance. We were reminded that it's really unclear what is going on after 48 weeks. We have to be careful about how this is portrayed and not simply stated that resistance does not exist to this drug.

Again brought up was the risks of stopping treatment, the fact that flares occur commonly up

to 25 percent of the patients, and the suggestion was made to monitor flares Q 4 to 8 weeks, but others felt even more strongly that stopping this drug carries some risks and that that warning should also be--it is part of the education mission to clinicians that there is that risk if you stop the drug.

Finally, drug-drug interactions, that these need to be carefully portrayed, again perhaps not as well understood as we would like them, and some of the drugs that were specifically mentioned - ddI, ibuprofen, HIV-PI, cyclosporine, and tacrolimus.

That brings us to our last question, Phase IV studies and, in particular, discuss the current program to detect the emergence of adefovir-resistant HBV and the optimal strategy of long-term resistance surveillance.

Let me take this question a little bit differently because we have been kind of throwing around ideas for Phase IV studies all day, so let me summarize what we have suggested up until now, both the sponsor, the agency, and the committee.

Five-year follow-up from the pivotal studies is something the sponsor recommended or is

doing right now. Also, follow-up of people who do convert their e-antigen to negative for five years.

We heard earlier today that increased representation of people of color, African-Americans and Latinos, is of importance. Special populations, pediatrics, the pregnant woman is another population that really hasn't been studied at all.

Establish the guidelines for decreased creatinine, as we have been talking about. HIV coinfection, I guess we have said that enough times today and, in particular, it was pointing out by Mr. Grodeck, administering adefovir with tenofovir since that is such a common agent in use today.

Again, Dr. Fletcher with drug interactions, we need some studies looking at the interaction with cyclosporine, tacrolimus, and perhaps some of the HIV-PIs.

Dr. Schapiro suggested additional resistance studies, and maybe we could spend a little more time on that.

People pointed out, or I guess the sponsor themselves said that the issue of relating drug levels to toxicity has not been well established, and that was an area that some around the table

felt would be helpful.

The whole concept of flares, of stopping, and what the significance of those was something that people were focused on, and then alternative dosing regimens and the applicability or the use of dose reduction with this drug was another area that people were interested in.

Before we turn to resistance, do people have other additions to that somewhat long list?

DR. STANLEY: Combinations.

DR. GULICK: Combination, thank you, so with lamivudine, which I think are planned already.

Dr. Englund.

DR. ENGLUND: Did you discuss when to stop? I mean how long is enough.

DR. GULICK: So, what is the durability and when can you stop the drug, always an interesting question.

Mr. Grodeck.

MR. GRODECK: If you take a look at the last few pages of the transcript from when lamivudine was approved for hepatitis B, you will see a pretty long and eloquent list of recommendations for combination therapy.

Here we are today, several years later,

with really no combination data in treatment-naive patients. This is several years down the road after this combination paradigm has been established, and yet we still don't have it. I wonder if there is a way to put bite in postmarketing recommendations to move forward combination therapies, because it is just not happening on their own. We know sequential monotherapy does not work. So, I hate to make that mistake again.

DR. GULICK: Dr. Brosgart, do you want to say something about that?

DR. BROSGART: I just wanted to add a clarification comment. We are interested in combination therapy, and those studies already are ongoing. We wanted to establish our target dose first. In collaboration with GlaxoSmithKline, we have an ongoing study in treatment-naive patients comparing the combination of adefovir plus lamivudine to lamivudine monotherapy.

Patients are just entering their second year of that study, and the first year data should be available probably early in the spring to late spring of next year, so that data will be emerging soon.

We have another study ongoing in Asia, which looks at the combination of adefovir plus FTC. We hope to shortly begin adefovir plus pegylated interferon studies.

There is a number of different studies that will be done in different populations, and those study designs are just being finalized, but they are kind of ready to take off. We have just had this other little thing we had to do first.

So, I wanted to reassure you that it wasn't just a lot of hot air this morning. Those studies are already well underway, and data will emerge soon.

DR. GULICK: Thank you.

Dr. Fletcher.

DR. FLETCHER: Carol, for example, on the study with GlaxoSmithKline, is that a two-arm or three-arm, in other words, is it lamivudine, adefovir, and then the combination together, or is it just a lamivudine versus adefovir plus lamivudine?

DR. BROSGART: Right, Dr. Fletcher, it is actually a two-arm study, and that study, the planning and the initiation of it was begun prior to the unblinding of our Phase III study, so we did

not have definitive data on our target registration dose, so at the time, that was an appropriate study to look at adefovir plus lamivudine versus lamivudine alone, which was the licensed agent as a comparator.

I am certainly sure that going forward, the study we are doing with FTC is adefovir versus adefovir plus FTC, so those in adefovir monotherapy arm there, but I am sure in Phase IV, as you know, once a drug is licensed, a lot of different kinds of combinations and strategies are employed.

DR. GULICK: Other suggestions for Phase IV? Dr. So.

DR. SO: No. Actually, since I have to run, I just wanted to put in a last word. I said that a couple of years ago in Lamivudine Advisory Board, but I would like to say this again.

Since a lot of these patients with chronic hep-B are in the developing world, I hope Gilead will try to make this available at an affordable price because I was recently in China, and at the moment, Epi-VHBV [ph], they sell it over there for $2.00 to $3.00 a day per pill, so basically it's $60, $90 a month, and a surgery resident only makes about $150 a month, so a lot of these drugs are

priced at a price which is beyond the reach of a lot of the potential patients, so I hope you would take that into consideration when you market the drug in Asia.

DR. GULICK: Let's swerve back to any more comments on Phase IV.

Dr. Stanley.

DR. STANLEY: Were you ready for resistance?

DR. GULICK: Yes, let's go.

DR. STANLEY: I just want to echo what Dr. Schapiro said earlier. In reading the planned studies in the book, there seems to be a dependence on genotypic evaluations, and I think we need to start with phenotypic evaluations now that you have that capability.

We saw data from four patients, and I think we need to be carefully evaluating phenotypically, and then we can get to the genotypic cause of it if we need to.

DR. GULICK: Dr. Schapiro, do you have other comments about the resistance plan?

DR. SCHAPIRO: Yes. I also think that it isn't going to look at all the patients, not to the selection, definitely looking at patients who are

rebounding and at different time points, and as Dr. Stanley said, the phenotypic techniques are important.

We won't go into the detail, but how exactly that is done is important because we only might cover the relevant part of the virus, but the second part, maybe Victor will allude to this, is we heard that no patterns were seen in conserved polymorphic regions, and again from our experience in other viruses, I think there maybe should be a systematic approach how that is looked at, and maybe again I will defer to Victor on that.

DR. DeGRUTTOLA: I will just comment briefly. I agree with Dr. Schapiro. I think it is good when presenting these analyses to comment on specifically what kinds of methodologies have been used to search for mutations that may be conferring resistance.

I actually think having the genotypic data and the phenotypic data at the same time can be useful for that purpose, and obviously, there is a distinction between exploratory analyses where you are searching for individual mutations or patterns and confirmatory analyses where you are trying to show that those are the ones that are important.

So, just encourage Gilead to try and use some systematic approaches, and the number published in the literature to do the search for the relevant mutations and then discuss specifically the methodology that is used.

DR. GULICK: Any last comments? Dr. Sun.

DR. SUN: Along the lines of resistance, it seems like the misallocation group, unfortunate though that is, offers a unique opportunity to look at resistance because if you, in fact, know what these patients got by mistake, and you have select patients who are on again, off again, on again, off again, and you can show that, in fact, that they did not develop resistance whether measured phenotypically or genotypically, that I think would be very reassuring in telling you something about what the barrier to resistance is for this compound in patients with essentially forced noncompliance on an interim basis, which is the worst possible case.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: When tenofovir was licensed, I was quite uncomfortable about having that compound used in treatment of HIV, knowing that it was very active against hepatitis B, but having

very little information about how to prudently use it since it was going to be used anyway.

So, I think it is relevant and important to know whether the company has intention to develop tenofovir as an HBV agent, and it relates to the issue of potency of the adefovir dose since you know where your dosing is not at the peak of the dose-response curve for obvious reasons.

It is my impression that a sister compound does not necessarily have that same limiting toxicity, at least from the data that you have shown us so far.

So, as you are talking about combination therapies with other compounds, one must ask what is the future of tenofovir as an HBV agent.

DR. GULICK: Dr. Brosgart, do you want to give us the inside scoop on that?

DR. BROSGART: Tenofovir and adefovir look very similar when you look at them in vitro. They are both active against wild-type, they are both active against lamivudine-resistant HBV, their in vitro profiles don't look different.

When we look at the clinical data that we have for tenofovir in treating HBV, we do not have data on patients who are non-HIV infected, but in

the coinfected patient who has been treated, either from the small group of patients who were coinfected in Study 907 or from an open-label study as part of the French early access program, and this is data that has accumulated on a total of about 25 patients.

At 24 and 48 weeks, the antiviral response, the decline in HBV DNA with tenofovir 300 mg is similar to that, that we see with adefovir 10 mg either out at 24 weeks or at 48 weeks.

So, in looking at the in vitro data and in looking at the in vivo data, there is not a suggestion that these two agents at least from the data we have are acting in a different way or that one appears to be more potent than the other, which one would have to have a really strong reason to want to develop a drug as a primary therapy in a new indication, and to go about doing that and actually testing tenofovir in the treatment of chronic hepatitis B, would only be warranted if it looked different from adefovir, and it look similar to adefovir.

So, we do not have plans to develop it as a primary therapy for chronic hepatitis B. Having said that, it does have activity against hepatitis

B, and we have a number of endeavors that are ongoing right now in the HIV coinfected population as part of our Phase IV commitment and also part of our large Phase IV program with tenofovir, evaluating tenofovir whether it's in patients who are naive, patients who are experienced, patients who are lamivudine-resistant.

Importantly, we have a prospective controlled study with the AIDS Clinical Trial Group, ACTG-5127, which is prospectively comparing adefovir to tenofovir, and that study should help the HIV treating physician have a better idea of when I have a patient who has lamivudine-resistant HBV, how does adefovir compare to tenofovir in that same patient population when they are matched for all characteristics.

So, that is the first controlled study we will have, and I am sure there will be other varieties of studies and data emerging on either tenofovir in coinfection or adefovir in coinfection, but based on the profile of tenofovir, I would not expect to look forward to a development program for tenofovir for the treatment of chronic hepatitis B in the non-HIV infected person.

DR. GULICK: Mr. Grodeck.

MR. GRODECK: One quick question. I wonder if tenofovir looks any safer than adefovir in terms of renal toxicity. In side-stepping, all of our issues about renal toxicity, you all gave approval to tenofovir, said it was safe. If the efficacy is the same, we are discussing renal toxicity, we could side-step it with tenofovir, it seems to me.

DR. GULICK: I guess the question to the sponsor theoretically, if tenofovir doesn't have nephrotoxicity, but what you just said was it has similar activity to adefovir, potentially, that is a benefit of tenofovir.

MR. GRODECK: Especially among patients who already have pre-existing renal issues.

DR. BROSGART: Tenofovir has not yet been studied in patients with renal impairment. Adefovir in patients with compensated liver disease, who entered study with normal renal function, through 48 weeks, there was not evidence of nephrotoxicity, and a substantial number of patients treated through 96 weeks, 1 out of 492 patients discontinued therapy for protocol-defined nephrotoxicity. This was a serum creatinine greater or equal to 0.5 mg/dL above baseline.

That value at the time of confirmation was 1.6 mg/dL. The patient discontinued adefovir and four weeks later had a normal serum creatinine, and it had resolved.

There is not evidence for accumulating nephrotoxicity with adefovir at the 10 mg dose in patients with normal renal function now, with a substantial number of patients not only treated to 48 weeks, but out to 96 weeks, and our long-term safety and efficacy studies that have been designed in consultation with the agency, will do much to establish what the profile is with long-term dosing up to five years.

There was much discussion this morning on a 0.3 mg/dL change, and what one saw through 48 weeks is a similar proportion of patients treated with placebo, had a 0.3 mg/dL change, as did the patients treated with adefovir.

Beyond 48 weeks, there is not a placebo comparator, and the patients who were described, the 29 patients, with a 0.3 mg/dL increase above baseline, included all of those patients who were described in the first year plus some additional ones in the second year, and those patients either resolved with continued dosing or stayed stable.

So, I think we have to refocus back onto the actual data that was presented and the data that was presented today shows that adefovir is a safe and tolerable drug through 48 weeks with a safety profile in the second 48 weeks that is similar to that in the first 48 weeks.

DR. GULICK: I don't want to open the door to a big discussion about what you just said, because this committee has already voted that we found adefovir safe, effective, and voted for the approval of the drug.

I guess if I can take a consensus of whispers and hisses around the table, people are suggesting that if there is any concern over renal toxicity with adefovir, yet the activity is very similar to tenofovir, and there is no worries about tenofovir with renal toxicity, that it would be reasonable to explore that. I am not sure we want to get into a big debate on that.

Drs. Birnkrant and Goldberger, did we do what you needed us to do?

DR. BIRNKRANT: You did an exemplary job, we really appreciate it, and we look forward to seeing everyone tomorrow at 8:00 a.m.

DR. GULICK: Let me thank the sponsor, the

agency, the members of the committee, and the observers for putting up with my back all day.

[Whereupon the proceedings were recessed at 5:35 p.m., to reconvene on Wednesday, August 7, 2002, at 8:00 a.m.]

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