DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

Friday, March 11, 2005

8:00 a.m.

Salons A and B
Hilton Washington DC North/Gaithersberg
620 Perry Parkway
Gaithersburg, Maryland

P A R T I C I P A N T S

Janet A. Englund, M.D., Chair

Anuja M. Patel, M.P.H., Executive Secretary

Committee Members:

John A. Bartlett, M.D.
Victor G. DeGruttola, Sc.D.
Douglas G. Fish, M.D.
John G. Gerber, M.D.
Richard H. Haubrich, M.D.
Victoria A. Johnson, M.D.
Robert J. Munk, Ph.D. (Consumer Representative)
Lynn A. Paxton, M.D., M.P.H.
Kenneth E. Sherman, M.D., Ph.D.
Eugene Sun, M.D. (Industry Representative)
Maribel Rodriguez-Torres, M.D.
Lauren V. Wood, M.D.
Ronald G. Washburn, M.D.

Special Government Employee Consultants (Voting):

Samuel K. So, M.D., B.S.
Kathleen Schwarz, M.D.

Government Employee Consultants (Voting):

Beth P. Bell, M.D., M.P.H.
Ronald Herbert, D.V.M., Ph.D.
Leonard B. Seeff, M.D.

SGE Patient Representative (Voting)

Brett Grodeck

FDA Participants:

Mark J. Goldberger, M.D., M.P.H., CDER
Debra B. Birnkrant, M.D., CDER
Linda L. Lewis, M.D., CDER
James G. Farrelly, Ph.D., CDER

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. ENGLUND: Good morning. Welcome, everyone. My name is Janet Englund. I am the acting chairperson today and I would like to welcome you to the Antiviral Drugs Advisory Committee.

Today we are going to discuss the new drug application 21-797 and 21-798 for entecavir tablets and entecavir oral solution, respectively, by Bristol-Myers Squibb Company. These drugs are proposed for the treatment of patients with chronic hepatitis B infection.

With that, I would like to call the meeting to order and introduce the committee members. In fact, I will have you introduce yourselves because that would be better. I would like to just remind everyone on this committee that this is being transcribed and so, before you speak, you are going to need to identify yourself but, for now, if we could just start maybe with Dr. Sun and just introduce yourself and your affiliation.

DR. SUN: Eugene Sun, Abbott Laboratories.

DR. GERBER: John Gerber, University of Colorado Health Sciences Center.

DR. WASHBURN: Ron Washburn, Shreveport VA and LSU.

DR. FISH: Douglas Fish, Albany Medical College, Albany, New York.

DR. HERBERT: Ron Herbert, National Institutes of Environmental Health Sciences and the National Toxicology Program.

DR. SHERMAN: Ken Sherman, University of Cincinnati.

DR. JOHNSON: Victoria Johnson, University of Alabama at Birmingham.

DR. PAXTON: Lynn Paxton, Centers for Disease Control and Prevention.

DR. WOOD: Lauren Wood, National Cancer Institute.

MR. GRODECK: Brett Grodeck, patient representative.

MS. PATEL: Anuja Patel, Executive secretary for the Antiviral Drugs Advisory

Committee, the Food and Drug Administration.

DR. ENGLUND: I am Janet Englund, from Children's Hospital and University of Washington, in Seattle.

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

DR. BARTLETT: I am John A. Bartlett, from Duke University.

DR. HAUBRICH: Richard Haubrich, University of California in San Diego.

DR. MUNK: Bob Munk, consumer representative.

DR. SEEFF: Leonard Seeff, Liver Disease Branch, NIDDK, National Institutes of Health.

DR. BELL: Beth Bell, Centers for Disease Control and Prevention.

DR. SCHWARZ: Kathy Schwarz, Johns Hopkins University.

DR. FARRELLY: Jim Farrelly, Division of Antiviral Drugs, FDA.

DR. LEWIS: Linda Lewis, Division of Antiviral Drugs, FDA.

DR. BIRNKRANT: Debbie Birnkrant, Division Director, Division of Antiviral Drugs, Food and Drug Administration.

DR. ENGLUND: And Dr. Mark Goldberger, from the FDA, will be joining us momentarily. At this point I would like to have Anuja Patel read for us the conflict of interest statement.

Conflict of Interest Statement

MS. PATEL: Thank you. The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda 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, with the following exceptions:

In accordance with 18 USC Section 208(b)(3), full waivers have been granted to the following participants, Dr. Johnson for her employer's contract with a federal agency to

provide virology laboratory support for the adult AIDS clinical trials group. The contract is funded for greater than $300,000 per year. Dr. Gerber for consulting on unrelated matters for the sponsor and a competitor. He receives less than $10,001 per year per firm. Dr. Bartlett for serving on speakers bureaus for two competitors. He receives greater than $10,000 from one firm and between $5,001 to $10,000 per year from the other. Dr. Sherman for serving on speakers bureaus for two competitors. He receives from $5,001 to $10,000 a year from each firm. Dr. Munk for consulting on unrelated matters for a competitor. He receives less than $10,001 a year.

Dr. Schwarz has been granted waivers under (b)(3) and 21 USC 355(n)(4) for her employer's grant to study competing products. Each grant is funded for less than $100,000 per firm per year. Dr. Haubrich has been granted a (b)(3) waiver for consulting on unrelated matters for a competitor and the sponsor. He receives less than $10,001 per year per firm. Brett Grodeck has been granted a

355(n)(4) waiver for owning stock in a competitor, valued at less than $5,001. Because the stock in a competitor does not exceed $25,000, 5 CFR 2640.202(a)(2) exception applies and a (b)(3) wavier is not required. Dr. DeGruttola has been granted a (b)(3) waiver for consulting on unrelated matters for two competitors. He receives less than $10,001 a year from each firm.

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.

We would also like to note that Dr. Sun has been invited to participate as an industry representative, acting on behalf of the regulated industry. Dr. Sun is employed by Abbott

Laboratories.

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

DR. ENGLUND: Thank you, everyone. With that done, I would like to introduce Dr. Debra Birnkrant who will now proceed to give us an overview of the issues and our plan for today.

Overview of Issues

DR. BIRNKRANT: Good morning. I would also like to welcome our advisory committee members and consultants to this meeting.

Today, as was mentioned, we will be discussing the new drug application for the tablet and solution formulations for entecavir for the treatment of chronic hepatitis B infection.

The last time this committee met to discuss a similar topic was back in 2002 when we presented the new drug application for adefovir, and on the second day of that meeting we discussed

general drug development for hepatitis B. Today's meeting gives us another opportunity to discuss this serious problem.

The next two slides were downloaded from cdc.gov. This slide shows the geographic distribution of chronic hepatitis B infection. What you can see in red are high andemic areas in Africa and Asia with hepatitis B prevalence at a rate more than 8 percent, and this is considered high. In gold we have medium prevalence areas, and in green we have low prevalence areas, such as the United States, excluding Alaska. In the high prevalence areas the lifetime risk of acquiring hepatitis B infection approaches 60 percent and is acquired mainly during childhood, whereas in the low prevalence areas the lifetime risk is much lower and occurs in adolescents, adults and well-defined risk groups.

This slide shows hepatitis B incidence by year through the years 1966 through 2000 in the United States. What this is dramatic for is the decline in hepatitis B occurring soon after

licensure of hepatitis B vaccine. You can see that the incidence drops dramatically over the years in the late '80s and beyond after public health programs adopted hepatitis B vaccination.

Although we see this dramatic decrease in the United States of acute hepatitis B it still remains a major problem. It has been estimated that chronic hepatitis B infection affects 350-400 million subjects worldwide and approximately 1.25 million subjects in the United States. It accounts for, it is estimated, approximately one million deaths per year due to complications of the disease, namely cirrhosis and hepatocellular carcinoma. The treatment options are quite limited. As you can see, there are only three at this point, interferon, lamivudine and adefovir dipivoxil.

I will briefly touch on the pros and cons of these therapies. Interferon is used in a limited patient population, however, it is used for a definite period of time and in the limited population the effect is durable. However, the

side effect profile is somewhat limiting. With interferon we see flu-like syndrome, depression, alopecia and exacerbation of autoimmune disorders.

Lamivudine, a nucleoside analog, is much better tolerated, however, subjects taking lamivudine develop resistance at a rate approaching 20 percent per year.

Adefovir dipivoxil, a prodrug of adefovir, a nucleotide analog, was approved in 2002. It is active against lamivudine-resistant virus, and is tolerated well except for nephrotoxicity that appears in decompensated patients, more so, and other advanced patients such as those undergoing transplant.

Let's turn now to today's subject, that is, entecavir. Entecavir is also a nucleoside analog. It has activity against HBV polymerase, and in vitro it inhibits lamivudine-resistant virus at concentrations 8-32-fold greater than that required for wild type virus.

Its antiviral activity has been demonstrated in established animal models. In

woodchuck, hepatitis virus infected woodchucks with that disease, 67 percent treated with entecavir survived 3 years compared to a 4 percent survival rate in infected historic controls. So, it appears quite active in this established animal model.

Now I will describe pertinent nonclinical pharm/tox findings briefly. There was an increased incidence of tumors in rodent carcinogenicity studies. Lung tumors were observed at low multiples of entecavir exposure relative to humans and it is thought that these tumors may be species specific. Other tumors occurred at much higher multiples of entecavir exposure relative to humans. This topic will be discussed extensively by Bristol-Myers Squibb and Dr. Farrelly of the Food and Drug Administration. What we have to keep in mind here is that the animal data needs to be interpreted in the context of the clinical data, the severity of the disease and the available treatment options. Turning to the clinical studies, I would like to commend Bristol-Myers Squibb for their drug development program for

entecavir. They studied a wide population in e-antigen positive, e-antigen negative and lamivudine-resistant subjects. Their trials were multicenter and multinational, using an active control, lamivudine. The endpoints used were similar to other approved therapies.

At today's advisory committee meeting we will be asking you to discuss the clinical trial data in the context of these animal carcinogenicity findings and the implications for human use. In addition, we will be asking you to discuss the adequacy of the proposed pharmacovigilance study. We will also pose a question related to pediatric usage.

If in the afternoon session when questions are posed you vote that this drug should be approved, we will then proceed to discuss labeling implications and further post-marketing studies.

With that, I would like to just briefly review the agenda. Following my comments, Bristol-Myers Squibb will present. This will be followed by a break. Then FDA will present and the

presentations will be discussed prior to lunch. At one o'clock there is an open public hearing. Following that hearing, we will continue the discussion and then pose our questions to the advisory committee. Thank you very much.

DR. ENGLUND: Thank you very much. Now I think we would like to begin with the sponsor presentation by Bristol-Myers Squibb.

Sponsor Presentation

Introduction

DR. SIGAL: Thank you, Dr. Englund and members of the committee and FDA. Good morning. I am Elliott Sigal. I am head of research and development and chief scientific officer for Bristol-Myers Squibb. Today it is our pleasure to bring you data on entecavir for the treatment of patients with chronic hepatitis B infection.

As you heard from Dr. Birnkrant, this disease affects well over actually a million people in the United States and accounts for approximately 5,000 deaths here a year. Outside the United States another 400 million people are chronically

infected with hepatitis B so it represents a worldwide public health issue of great importance.

We, at Bristol-Myers Squibb, have concluded, based on the data you will hear today, that entecavir represents an important therapeutic advance. Our application is being considered first here, in the U.S., but we have filed in Europe and in China, and intend to file elsewhere around the world as part of a larger global commitment.

All new therapies present a need to assess both benefits and risks. Years ago, knowing this compound to be a nucleoside analog, we intentionally completed and analyzed rodent carcinogenicity studies before initiating a Phase III program. Then we continued to explore the mechanisms of these rodent findings and we collaborated with health authorities around the world on how to characterize clinical benefit. The goal has been to determine benefits seen in the clinic and weigh those against the potential for risk raised by nonclinical studies.

Entecavir has clinical benefits based on

its antiviral potency and these are superior suppression of viral replication; a favorable resistance profile; and improvement in both liver histology and in biochemical abnormalities. To establish all of this we conducted an extensive Phase III program, the first in this field with an active comparator. As the sponsor, we concluded that the benefits in the clinic, including the resistance profile, outweigh the potential seen of risk in nonclinical studies and entecavir, to us, represents an important therapeutic option for patients with chronic hepatitis B infection.

However, as with any new medicine, an assessment of benefit-risk at the time of approval can only be an estimate. Therefore, our company is committed to further defining therapeutic benefits and to understanding any potential human risk with entecavir.

To accomplish this we have submitted to FDA draft pharmacovigilance plans, approaches and observational studies that we plan to conduct to allow for a continuous benefit-risk assessment once

entecavir is available for patients. For the medical community these studies will advance the overall scientific knowledge about this disease. Bristol-Myers Squibb has a history of antiviral clinical research in the treatment of patients with HIV infection. Now with entecavir we are expanding that commitment to advance the medical science of chronic hepatitis B infection.

Furthermore, let me say that our efforts in the marketplace will be directed to ensure the appropriate use of this new medicine. We will create a U.S. field organization solely dedicated to entecavir. It will combine medical professionals and representatives who will be specifically trained in chronic hepatitis B. Their focus will be on a relatively small number of physicians, 3,500, that provide care for nearly all the U.S. patients treated for chronic hepatitis B. This focused approach will ensure high quality interaction with prescribing physicians and appropriate use of entecavir for patients.

Dr. Rich Colonno will now begin the data

presentation. Dr. Englund, two of our speakers fell ill over the last 36 hours so you will see a few different names on the program. One of our internal hepatologists, Dr. Atillasoy, will be the one presenting our clinical data. Dr. Colonno?

Background

DR. COLONNO: Good morning. Sorry for the confusion. Entecavir is under review for the proposed indication shown here, the treatment of chronic hepatitis B disease in adults with evidence of liver inflammation. The usual dose will be 0.5 mg daily and a higher 1.0 mg dose is proposed for patients who are lamivudine-refractory.

Our presentation will follow the outline shown on this slide, covering nonclinical safety, clinical efficacy, clinical safety, resistance and pharmacovigilance. We have been assisted in evaluating our data by a number of experts who are listed on the next slide. These consultants, covering hepatology, health policy, toxicology, pathology and biostatistics, are here and available to the committee.

Dr. Birnkrant and Dr. Sigal outlined the disease burden and consequences of chronic HBV infection. Only about 10-30 percent of people

currently affected with HBV go on to develop a chronic infection. But the millions who do, it is sometimes decade-long process that for a substantial number of patients ends with cirrhosis, liver failure, hepatocellular carcinoma, transplant or death.

This is a viral disease and the clinical course of liver injury is driven by the continuous replication of the virus perpetuating a cycle of inflammation. HBV is not inherently cytopathic but liver cells support a continuous cycle of viral replication that triggers the inflammatory response that over time leads to fibrosis, cirrhosis and liver cancer. HBV has recently been designated a carcinogen, in recognition that HBV-induced hepatocellular carcinoma is the fifth most frequent single type of cancer.

It has now been shown that the outcome of this long course of chronic infection with HBV is

not just caused by the initial infection but is related to the degree of continued viral replication. This was supported by a prospective Taiwan cohort study in which three key points emerged: The incidence of hepatocellular carcinoma and liver cirrhosis correlated with baseline HBV DNA levels. The higher the baseline, the higher the incidence. Two, persisting elevation of the viral load over time has the greatest impact on hepatocellular carcinoma risk. Viral load predicted risk of future hepatocellular carcinoma independent of e-antigen status and serum ALT levels.

The concept that viral replication drives disease process is depicted in the schematic shown on this slide. Viral replication, monitored by serum HBV DNA levels, drives the downstream inflammation, measured by ALT levels and by histology assessments. These were our week 48 endpoints, and we will be referring to this simplified schematic later in our presentation.

Currently, three drugs are approved to

treat chronic hepatitis B infection, interferon, lamivudine and adefovir. Interferon is an immunomodulator while adefovir and lamivudine are antivirals whose demonstrated antiviral activity led to their approval. In their clinical studies both lamivudine and adefovir were shown to be superior to placebo using the endpoints of liver histology, viral suppression and ALT normalization at week 48. They decreased viral load, the first stage of the schema, and interrupted the process measured by ALT and histology, in the center section. Beyond the week 48 data points, lamivudine has now shown superiority to placebo in affecting some of the long-term outcomes seen in the far right-hand slide of the schema, characterized as disease progression.

In the recent landmark paper by Liaw et al., lamivudine treatment was prospectively compared with placebo in patients with compensated cirrhoses who are at greatest risk for disease progression, including HCC and worsening cirrhosis. With lamivudine treatment by 32 months the rate of

disease progression was significantly reduced relative to placebo, 8 percent versus 18 percent. This study confirmed the hypothesis that effective antiviral therapy results in a better long-term clinical outcome than indicated by the week 48 histology, virology and ALT endpoints.

The study also pointed out that a development of resistance to a particular antiviral therapy limits its benefit. By the end of the study roughly half of the lamivudine-treated patients who had developed lamivudine resistance, or YMDD virus, and these patients had twice the percentage of disease progression when compared to those where the virus remained fully susceptible, 11 percent versus 5 percent respectively.

So, while lamivudine is effective and lacks the tolerability concerns of interferon and, unlike adefovir, does not require careful monitoring of renal function, resistance impacts the ability of lamivudine to deliver long-term benefits. While the study confirmed that antiviral treatment provides benefit, it also suggested that

a more effective antiviral with both greater potency and less resistance will be more efficacious in preventing downstream clinical disease.

This morning you will see that entecavir, by the accepted and proven histologic, virologic and biochemical endpoints of our studies, was superior to lamivudine. We will demonstrate that entecavir is effective, safe and well tolerated; has excellent potency and very low rates of resistance; and maintains future options because it doesn't select for lamivudine or adefovir resistance and is, therefore, an important advance in therapy for chronic HBV disease.

The activity of entecavir results from its being a cyclopentyl guanosine analog. It is a selective and potent inhibitor of HBV replication. It has no significant activity against HIV. The selectivity contributes to its safety since it is a poor substrate for sailor DNA polymerases and does not inhibit human mitochondrial or gamma polymerase. Its potency reflects the fact that it

inhibits all three functional activities of the HBV polymerase, priming, DNA-dependent synthesis and reverse transcription. It is also a function of a highly efficient conversion of entecavir to its active form entecavir triphosphate, seen consistently in a wide variety of cell types.

Entecavir undergoes rapid and efficient phosphorylation by sailor enzymes at low concentrations, and can be detected within one hour. Once formed, the intracellular half-life of entecavir triphosphate is approximately 15 hours.

With an EC 50 of 4 nM it is the most potent inhibitor of hepatitis B virus. Entecavir is greater than 300 times more potent than either of the available agents, lamivudine or adefovir, or two newer agents under development dibividine[?] and tenofovir.

Animal models of HBV have been developed using woodchucks and ducklings and entecavir demonstrated impressive potency in these systems as well. The woodchuck model is of particular importance because it has been predictive of the efficacy and safety of drugs subsequently used in

humans to treat hepatitis B virus. The antiviral susceptibility of the woodchuck hepatitis B virus, or WHBV, is similar to the human virus. In this model greater than 95 percent of chronically infected animals will development HCC and die, and less than 5 percent will survive to age 4.

In our study, animals standard established chronic infection were dosed with entecavir at 0.5 mg/kg, a dose that results in exposure levels of approximating the exposure in humans with the 1 mg dose. The drug was initially administered daily for 2 months and then weekly for a total of 14-36 months. In both groups entecavir treatment resulted in viral DNA levels being reduced by as much as 8 logs to undetectable levels. The reductions were sustained for up to 3 years, with no evidence of virologic rebound or resistance.

The study compared the improvement in survival versus historical controls, shown in grey. The 11 woodchucks, represented by the yellow bars, started treatment at 8 months of age as soon as a chronic infection was verified. They had 4-year

HCC-free survival of 50 percent and 80 percent respectively for the 14- and 36-month treatment groups. The non-concurrent historical control had a survival rate of 4 percent. Although the numbers of animals were small, these results were of high statistical significance. Surviving animals were also shown to have no histological evidence of HCC development upon subsequent examination.

In summary, the nonclinical data and the expected benefit of antiviral treatment supported going forward with development of entecavir for treatment of chronic HBV infection. As with any drug being developed for long-term chronic dosing in humans, the carcinogenicity potential of entecavir was evaluated in lifelong dosing studies in rats and mice. Dr. Lois Lehman-McKeeman will now present this data.

Nonclinical Safety

DR. LEHMAN-MCKEEMAN: Today's discussion of the nonclinical safety of entecavir is focused on the rodent carcinogenicity studies. Entecavir was identified as a carcinogenic hazard in rats and

mice, and the benefit-risk evaluation for entecavir must consider this risk identified in animals relevant to the human clinical benefit.

For background on the rodent data, I will briefly describe the design, conduct and interpretation of these studies. Rodent carcinogenicity studies are lifetime studies, typically 2 years, and group sizes are large with 50-60 animals per sex per group. Dose selection is critical, and highest dosage is expected to represent a maximum tolerated dose, or MTD. The simplest definition of an MTD is a dose that causes no more than a 10 percent decrease in body weight gain relative to controls. The lower dosages studied, typically 2 additional levels, are selected to be some fraction of the MTD or some multiple of the relevant human clinical exposure.

At the end of the study all tissues are evaluated microscopically for tumors. Several tissues in rats and mice are prone to spontaneous tumor development. For example, in mice there was a relatively high background rate of tumors in

liver and lung, while in rats liver, pituitary and mammary gland tumors occurred at high spontaneous rates. So, finding tumors in animals, including controls, is not surprising and we rely on statistical methods and an understanding of historical control tumor rates to identify those that are drug related.

Statistical significance in rodent tumors is established by sequentially testing for a linear dose-dependent trend starting with all dose groups. Tumor incidence is adjusted for survival and the time and cause of death and the level of statistical significance varies with whether a tumor is common or rare. The more common the tumor, the more rigorous the statistical analysis. When the results identify a positive trend, data are reanalyzed by dropping the highest dose and repeating the test. This cycle is repeated until no significant trend is observed.

With that as an overview on rodent carcinogenicity studies, let's review the results for entecavir. These results have been reviewed

with the FDA's Executive Carcinogenicity Assessment Committee, or CAC, and the full CAC and a number of tumor sites were concluded to be relevant to human safety.

Entecavir-induced tumors followed two distinct patterns. The first pattern was observed in tissues that showed preneoplastic changes, that is, sites were early changes, consistent with the increased likelihood of tumor development, were observed. The only site that showed this pattern was the mouse lung.

The second pattern of increased tumors was in tissues that showed no evidence of preneoplastic changes and occurred at high exposure multiples relative to anticipated human exposure. These tumors included liver carcinomas in male mice; vascular tumors in female mice; gliomas in male rats; and gliomas, liver adenomas and skin fibromas in female rats.

In addition to listing the tumor sites, let's look at the incidences observed in these studies. Entecavir was dosed to mice across a dose

range of 0.004 mg/kg to 4 mg/kg. To orient you to this slide, the dosages are shown in the top line and the exposure multiples are noted below the dosages representing the comparison of the plasma area under the curve in mice relative to human exposure at the 0.5 mg or 1 mg dose. The exposures are presented as those in the males, followed by the females. 4 mg/kg was an MTD and this dose represented at least a 40-fold multiple over the human exposure at 1 mg.

The mouse lung is a major target organ for tumor development following entecavir treatment. Lung tumors are common in mice. There was a 12 percent incidence of tumors in the control males in this study.

Entecavir increased the incidence of lung adenomas with a statistical increase in tumors, here noted in yellow, observed at the 0.4 mg/kg dose in males. This dose is 3-5 times higher than human clinical exposure. Lung adenomas were further increased at the 2 higher dosages and at 4 mg/kg entecavir increased the incidence of lung

carcinomas.

In female mice lung tumors occur at a higher spontaneous rate than in males, with a background incidence of 20 percent in this study. Entecavir increased pulmonary tumors in female mice but the statistical significance was noted only at the highest dose.

Other toxicology studies indicated that entecavir elicited unique changes in the mouse lung, and we conducted experiments to define these changes and to determine whether they were linked to the increased susceptibility to tumor development. The results showed preneoplastic changes in the mouse lung that consisted of increased numbers of macrophages and Type II pneumocyte hyperplasia. Cell proliferation is a recognized risk factor for tumor development and entecavir caused a sustained proliferation of Type II pneumocytes. Most mouse lung tumors arise from Type II pneumocytes and these cells were identified as the progenitor cells for entecavir-induced lung tumors as well. The increased numbers of

macrophages was required to support the proliferation of the Type II pneumocytes and entecavir increased the number of alveolar macrophages in the lung because it was chemotactic for mouse monocytes.

In contrast to the mouse, no similar changes were observed in the lungs of rats, dogs or monkeys treated with entecavir. Finally, although entecavir was chemotactic for mouse monocytes, it was not chemotactic for human monocytes, suggesting that an accumulation of macrophages in the human lung would be unlikely to occur. The results suggest that entecavir causes unique effects in the mouse lung and lung tumors observed in mice may be species specific.

The second presentation of entecavir-induced tumors in mice was in organs that, unlike the lung, showed no evidence of preneoplastic change. In males entecavir increased the incidence of liver carcinomas and in females entecavir increased the incidence of vascular tumors, specifically hemangiomas. In both cases there was

no dose response relationship noted, with tumors observed only at the highest dosage.

We have not explored mechanisms underlying the high dose tumor findings on an organ by organ basis, but we have looked at whether a common mode of action may contribute to tumor development. Entecavir is phosphorylated to entecavir triphosphate, the active form that inhibits viral replication, and we determined that, likely by competing for phosphorylation as depicted here, entecavir disrupts deoxynucleotide triphosphate pools, dNTP pools, in male mouse liver. Data in the scientific literature demonstrates that such perturbations disrupt the fidelity of DNA synthesis and repair. We conclude that changes in the dNTP pools may explain tumor findings, particularly when there is a high dose response for tumor development.

Moving on to rats, in Sprague-Dawley rats entecavir was dosed to males at dosages up to 1.4 mg/kg or to females at dosages up to 2.6 mg/kg. The 4 dosage levels are noted here along with the

exposure multiples as were presented on the mouse slides relative to the 0.5 mg or 1 mg clinical dose. Maximum exposures were at least 35 times human exposure in male rats or 24 times human exposure in female rats. In rats all tumors observed were consistent with the second pattern of tumor presentation, that is, no evidence of development of preneoplastic change.

In males and females entecavir increased the incidence of gliomas with statistical significance only at the highest dosage. In females entecavir increased the incidence of liver adenomas and skin fibromas. As determined in mice, we have postulated that the dNTP pool perturbations resulting from high doses of entecavir that overwhelm the strict regulation of nucleotide metabolism may explain entecavir-induced tumors in rats.

Carcinogenicity studies in rodents identify whether a compound is a carcinogenic hazard. In the absence of data in humans it is assumed that carcinogenic effects in rodents

suggest a possible carcinogenic risk in humans. However, to extrapolate these findings to humans other relevant data, such as genetic toxicity and species differences in biological response, along with dose-response relationships and exposure comparisons, are important considerations that may increase or decrease the likelihood of human cancer risk. For entecavir there is evidence suggesting a unique biological response in the mouse lung and mouse lung tumors may be species specific.

Extrapolation of the other tumor findings is more difficult, but the weight of evidence suggests that human risk is minimal because rodent tumors were observed at dosages that greatly exceed human clinical exposure.

Dr. Evren Atillasoy will now review the benefit of entecavir as determined from the Phase III clinical trials.

Clinical Efficacy and Safety

DR. ATILLASOY: Thank you and good morning. The entecavir clinical development program is comprehensive and assesses the efficacy

and safety of entecavir for the treatment of chronic hepatitis B infection. The experience was broad with major disease patterns well represented. Studies addressed hepatitis B e-antigen positive patients and e-negative disease, and assessed entecavir in lamivudine-refractory as well as nucleoside-naive patients.

The global program recruited patients from 5 continents in over 30 countries. Separate programs are in progress in China and Japan. The studies that contribute to the NDA review provide analyzed data on approximately 1,500 entecavir-treated patients. Entecavir is the first nucleoside program to be evaluated for HBV using an active comparator, lamivudine, which was the only approved HBV nucleoside at the time that the program was initiated.

The map of the clinical program illustrates the sense of the size, breadth and complexity. The core of the program is represented by the green box and includes the three Phase III studies you will be hearing about today. Small

studies in special populations include experiences in liver transplant patients, co-infected HIV-positive patients and decompensated patients, the trial which we are still actively enrolling.

Two long-term rollover studies provide for prolonged observation and data collection. Study 901, at the bottom left, provides an ongoing treatment option for those patients in whom long-term treatment is appropriate. Study 049 is a post-treatment observational study, designed to collect long-term safety and efficacy information. All Phase III patients have the opportunity to enroll in these trials. These data in 049 have not yet been analyzed.

Dose selection for entecavir anticipated that lamivudine-refractory patients would require a higher dose than naive patients because of the higher EC 50 of lamivudine-resistant virus in vitro. An earlier proof of principle study testing doses over a range from 0.5 mg to 1 mg daily hinge on overlapping responses for the highest doses of 0.5 mg and 1 mg daily. Therefore, these doses were

used as the highest ones tested in dose selection studies, 0.5 mg in naive patients, in yellow on the left graph, and 1 mg refractory patients, in orange on the right graph. The lamivudine control is represented in blue in both graphs.

A dose response was demonstrated in each population, with the greatest responses occurring at the two highest doses with diminishing incremental benefit at the last increase. Entecavir 0.5 mg daily and 1 mg daily were taken forward as the doses to be tested for Phase III for naive and refractory patients respectively.

Clinical efficacy--Phase III included trials in three disease settings, nucleoside-naive e-antigen positive patients, nucleoside e-antigen negative patients and lamivudine refractory e-antigen positive patients. The definition of lamivudine refractory was that patients must have clinical failure after at least 6 months of lamivudine, or earlier failure with the confirmation of lamivudine-resistant virus. Clinical failure was defined as detectable viremia

using the bDNA assay. Today's presentation of clinical results will be by treatment population rather than study number.

Lets turn to study design across Phase III. Patients were screened and randomized 1:1 to either entecavir or lamivudine in a double-blind fashion and were treated for a minimum of 52 weeks. Lamivudine-refractory patients who were required to have breakthrough viremia while on lamivudine were switched on treatment day 1 directly from lamivudine to blinded study drug without a period either of overlap or washout. Liver biopsies were obtained at baseline and at week 48 for assessment of the primary efficacy endpoint, histologic improvement. Patient management at week 52 was based on lab results using data from the week 48 visit, with results of the 24 follow-up period presented in the briefing document that you have.

Inclusion criteria, let's talk about these for the three studies. Inclusion criteria required that patients needed to have compensated liver disease, together with an elevated ALT, or were

required to have detectable viremia by bDNA. The different virologic characteristics of the e-antigen positive and e-antigen negative disease patients resulted in different minimal requirements for enrollment by HBV DNA.

The baseline demographics of each study population are consistent with the characteristics expected for the patient population. In the presentations that follow results for the naive e-antigen positive patients will appear on the left of the slide. In the middle you will see data for the naive e-antigen negative patients and on the furthest right you will see results for the lamivudine-refractory e-antigen positive population. Within each study the entecavir/lamivudine study groups were well matched for demographic characteristics.

Turning to baseline HBV characteristics, these are also expected to differ according to the pattern of disease studied. Again, within each study the entecavir/lamivudine treatment groups were well matched for baseline HBV disease

characteristics. Looking across studies, HBV e-antigen positive patients, whether nucleoside-naive or lamivudine-refractory, had mean HBV DNA values that were approximately 2 logs higher than the mean value for the e-antigen negative population.

Finally baseline histology across the studies showed a higher mean necroinflammatory score, using Knodell, than nucleoside-naive subjects. Only a minority had biopsy evidence for cirrhosis as classified by Knodell fibrosis score of 4. This is because participants were selected to have compensated liver disease.

Patient disposition--patient disposition for the first 48 weeks across the three studies demonstrates high retention rates, with at least 94 percent of entecavir-treated patients completing 48 weeks of treatment in each of the three studies. Lamivudine retention rates ranged from 87-95 percent, with the lowest rate in the lamivudine-refractory study.

In all three studies, paired biopsies were

scored using a single reader, who was Dr. Zachary Goodman. Dr. Zachary Goodman was blinded to drug assignment as well as the temporal sequence of the paired biopsies. Dr. Goodman also read the biopsies for lamivudine and adefovir registrational programs.

Overall, paired baseline and week 48 biopsies were available for efficacy assessment in 88 percent of patients. Histologic improvement at week 48 as compared to baseline is the primary efficacy endpoint in these trials. Histologic improvement was defined as at least a 2-point reduction in the Knodell necroinflammatory score with no concurrent worsening in Knodell fibrosis.

In order for a biopsy pair to be evaluable, the baseline sample must have had enough tissue pathologically and it also must have had a necroinflammatory score of at least 2, and 89 percent of patients had a baseline biopsy that fit these criteria and constitute the evaluable baseline histology cohort. Patients from the evaluable cohort who had missing or inadequate week

48 specimens were considered to have no improvement. Therefore, the primary analysis for histologic improvement is analogous to a non-completer or equal failure analysis but is applied to the evaluable cohort rather than the all-treated population.

The nucleoside-naive studies were designed with two-stage testing. The first test was for non-inferiority and, if that was met, then superiority was tested. Non-inferiority is established if the lower confidence limit is above minus 10 percent. Superiority is met if the lower confidence limit is above zero. In comparing two active treatments it was expected that differences in histologic improvement, a downstream endpoint, might take longer than 48 weeks to emerge. Nevertheless, at week 48 entecavir 0.5 mg daily was superior to lamivudine 100 mg daily for histologic improvement in both nucleoside-naive populations. Entecavir achieved a 72 percent response rate in naive e-antigen positive patients and a 70 percent response rate in the naive e-negative population.

Looking to the study in lamivudine-refractory patients, this was designed for superiority. Two independent co-primary

endpoints were evaluated because histologic response hadn't been characterized in this population previously. The first co-primary endpoint is histologic improvement, as we have discussed. The second is a composite reflecting both virologic response and hepatic inflammation as measured by serum ALT. Entecavir 1 mg daily was superior to continued lamivudine 100 mg daily for both co-primary endpoints, and 55 percent achieved the endpoint of histologic improvement; likewise, 55 percent achieved an HBV DNA below the detection of the bDNA assay, together with an ALT less than 1.25 times the upper limit of normal. Changes in fibrosis are expected to follow changes in necroinflammation. While the primary endpoint, histologic improvement, assessed primarily necroinflammation, secondary histologic endpoints included an assessment of changes in fibrosis using the Ishak scoring system.

The numbers in the circles along the zero line represent the proportions with no change, while the bars above and below the line represent the proportions with improvement and worsening respectively. In the two naive studies entecavir and lamivudine are comparable. This is not

unexpected as week 48 is relatively an early time point for assessing this downstream endpoint, especially when comparing two active treatments. The effect of large differences, however, can be seen in lamivudine-refractory patients. Here entecavir was superior to lamivudine for improvement in fibrosis. The distribution of responses in entecavir-treated patients mirrors that in the naive studies and 34 percent had improvement while only 11 percent worsened while on entecavir. This compares to only 16 percent improvement and 26 percent worsening for continued lamivudine.

Non-histologic secondary endpoints were also assessed at week 48. These included virologic, biochemical and serologic endpoints.

These assessments are all used routinely in the clinical management of patients with chronic HBV. Treatment comparisons were made using a non-completer or equal failure analysis, and all treated patients were counted in the denominator.

Results for virologic endpoints demonstrate superiority for entecavir in all three populations studied. The proportion of patients achieving an HBV DNA less than 400 copies/mL by PCR is presented here as a function of time on treatment, and 69 percent of naive e-antigen positive patients treated with entecavir achieved an HBV DNA of less than 400 copies/mL as compared to 38 percent for lamivudine, an absolute difference of 31 percentage points.

The lower baseline viremia and e-antigen negative patients is associated with higher rates of viral suppression. Here, 91 percent of entecavir-treated patients achieved an HBV DNA less than 400 copies as compared to 73 percent for lamivudine, an absolute difference of 18 percentage points. In both populations there is an early

separation response, with superiority for entecavir as early as week 24. This was the first time point in which a PCR measurement was taken.

In the lamivudine-refractory population entecavir was also superior to continued lamivudine, with early separation during the first 24 weeks of treatment, and 21 percent of entecavir-treated patients achieved an HBV DNA less than 400 copies.

An additional way of assessing virologic response is looking at the mean log reduction in HBV DNA from baseline. For this analysis results depend upon the characteristics of the population studied and the HBV DNA used. The maximum reduction possible for a particular population depends on the starting baseline values for those individuals. In a responder the endpoint will reflect the lower limit of detection for an assay. Therefore, comparisons of this endpoint across different populations must account for differences in baseline characteristics and HBV DNA assay.

Entecavir is superior to lamivudine across

all three populations. Naive e-antigen positive patients who started out with an HBV DNA of 9.7 logs in wild type virus demonstrate--so that entecavir demonstrates its full potential with a mean decrease of nearly 7 logs at week 48, differing by 1.5 logs or 30-fold from lamivudine. In the e-negative population the 5-log decrease for entecavir approximates the maximal change possible given the lower starting HBV DNA and the PCR limit of quantitation at 2.5 logs, or 300 copies/mL. In the lamivudine-refractory population entecavir achieves a substantial 5.1-log decrease in HBV DNA.

Viral suppression also leads to reduced hepatic inflammation as judged by ALT. Here, entecavir is superior to lamivudine for normalization of ALT in all three populations. As expected, the largest treatment difference is seen in the refractory population.

Reduced viral replication may also induce an immunologic response resulting in HBe antigen seroconversion. The precise biology of this interaction is poorly understood. In the naive

e-antigen population entecavir and lamivudine are comparable for seroconversion with response rates of 21 and 18 percent respectively.

In summary, across the three Phase III studies entecavir is consistently superior to lamivudine for histologic improvement, virologic response and ALT normalization. For the four key endpoints across the three studies there were 11 efficacy comparisons. Entecavir demonstrates statistical superiority to lamivudine in 9 of these 11, with confidence intervals for treatment differences lying to the right of zero. The two seroconversion endpoints favor entecavir numerically and establish non-inferiority with confidence intervals lying above the minus 10 boundary. In addition, the mean log reduction is consistently superior for entecavir, ranging from 5-7 logs across the three populations.

Let's move to safety. The clinical profile of entecavir has been extensively characterized. The format for the safety presentation will differ slightly from that of the

efficacy presentation. These analyses use augmented patient cohorts and integrate data across studies in order to increase the sensitivity to possible safety signals.

The nucleoside-naive lamivudine-refractory populations are considered separately, primarily because the exposure to entecavir differs with dose. The safety cohort includes patients from 10 analyzed Phase II and Phase III studies. For the Phase III populations mean treatment duration was 5 weeks longer for entecavir-treated naive patients and 17 weeks longer for entecavir-treated refractory patients. The follow-up observations were consistently longer for entecavir than for lamivudine across all populations.

Follow-up is defined as the period of post-treatment follow-up during which no alternative HBV therapy was given. Its duration was shorter in refractory patients as compared to naive patients due to earlier initiation of alternative therapy or early enrollment into an entecavir rollover trial. Observation periods for

the safety cohort are expanded to include open-label treatment and post-treatment observation on alternate HBV therapy.

The safety presentation is divided into three sections, general safety, hepatic safety and malignant neoplasms. General safety analyses provide standard assessments for rates of clinical adverse events and laboratory abnormalities. All analyses use data from all treated patients in the selected studies. Analyses are cumulative from the first day of dosing through the last contact with each patient. Therefore, year 2 data are included for some patients.

Rates for three standard safety assessments--discontinuations due to an adverse event, serious adverse events and deaths, were low for both treatments across both populations. The types of serious events reported for entecavir and lamivudine were comparable, and no individual serious adverse event occurred in more than one percent of patients. None of the events leading to death was considered related to study drug.

In terms of adverse events, on treatment adverse events were generally mild to moderate in severity and were common, reflecting the long

duration of study observation. The frequencies of individual events and the types and distribution of these events were comparable for both treatment groups across both populations.

Hepatic safety--hepatic safety focuses on hepatic flares because these can represent an important clinical risk in the treatment of hepatitis B regardless of the specific therapy which is used. ALT flares were defined as increases in ALT greater than 10 times the upper limit of normal and 2 times the patient's own reference value. The reference value was the baseline value for on-treatment flares. For off-treatment flares the reference was the lower of the baseline or the end of treatment value.

Rates for on- and off-treatment flares are consistently less than 10 percent for entecavir. Of note, the median time from stopping therapy to an off-treatment flare is substantially longer for

entecavir. The delayed time course for off-treatment flares for entecavir may be related to the extent of virologic suppression achieved on treatment.

ALT flares are frequently asymptomatic. A deterioration in hepatic function can, however, occur without ALT changes that meet this flair definition. Therefore, we performed analyses to identify individuals meeting flair criteria who had associated relevant laboratory abnormalities or relevant hepatic clinical events, or those who had a serious hepatic adverse event without meeting flair criteria. These events were infrequent among both naive and refractory patients, with the number of individual cases summarized here.

Safety surveillance of the entecavir development program involved the assessment of comparative incidences for new or recurrent malignancy diagnoses in entecavir- and lamivudine-treated subjects. Use of the larger safety cohort database increases sensitivity in this analysis of events that are infrequent. A new

diagnosis or a new recurrence of malignancy was counted from the time of first study dose to the time of the last patient contact regardless of whether the event was diagnosed on or post treatment. In the safety cohort the entecavir/lamivudine treatment groups differed in size and the duration of observation.

Event rates are presented as incidences of patients diagnosed per 1,000 patient-years of observation. Hepatocellular carcinoma is the single most frequent type of cancer identified, not unexpectedly, due to the underlying HBV disease. Incidences across the treatment groups are comparable whether assessed for any malignancy, any malignancy excluding non-melanoma skin tumors or the category of great interest, non-hepatocellular carcinoma, non-skin malignancies.

Further analyses in the entecavir program demonstrate that the distribution of new or recurrent non-skin malignancy diagnoses over time is comparable for entecavir and lamivudine. In both treatment groups the greatest number of new

diagnoses occurred between weeks 24 and 48. This temporal clustering may reflect tumors that were latent at the time of study enrollment. There is an apparent leveling off for new diagnoses after week 48.

In order to establish a comparative context for the observed tumor rates in the development program, Bristol-Myers Squibb provided grants to two independent research groups. These groups identified cohorts of chronic HBS antigen positive patients within their established databases. The results are provided in the two right-hand columns. The Taiwan cohort had been prospectively identified as part of an established cancer incidence study which started in 1991 and is sponsored by the Taiwan Ministry of Health. The rates of malignancy in the entecavir-lamivudine arms are comparable to the Taiwan and the Kaiser observational cohorts.

In summary, the safety profile of entecavir is consistently comparable to that of lamivudine. Also, the safety of entecavir is

comparable across the nucleoside-naive and lamivudine-refractory populations, and across the two doses of 0.5 mg and 1 mg daily. Importantly, the malignancy incidences among approximately 1,500 entecavir-treated patients are comparable among those observed in the lamivudine-treated control group. Dr. Richard Colonno will now present the resistance profile for entecavir.

Resistance

DR. COLONNO: Thank you. For all antivirals there is a direct relationship between potent viral suppression and absence of viral resistance emergence because viruses require a minimal threshold level of replication to select for resistant variants. Sustained suppression of viral DNA undetectable levels in the woodchuck model, described earlier, resulted in the absence of virologic rebound and no evidence of resistance over the 14- and 36-month treatment periods.

To ascertain whether the potent and sustained suppression of viral replication achieved by entecavir in our clinical studies results in a

favorable resistance profile, a comprehensive resistance evaluation was conducted that included both in vitro and in vivo studies, along with characterization of over 1,500 clinical samples from entecavir-treated patients.

In vitro studies showed entecavir susceptibility was reduced when viruses contained the two primary lamivudine-resistant substitutions, a leucine thymodin[?] change at residue 180 and a methionine to valine or isoleucine change at residue 204. Despite this reduction, entecavir remains greater than 50-fold more potent than adefovir against lamivudine-resistant viruses. There was no cross-resistance between entecavir and adefovir since adefovir-resistant viruses containing resistant substitutions at residues 181 or 236 remain fully susceptible to entecavir.

During Phase II studies two extensively pretreated patients, designated as patient A and patient B, exhibited virologic rebounds on entecavir therapy. Following at least 76 weeks of entecavir, virologic rebounds noted in two patterns

of genotypic resistance emergence were identified. Entecavir resistance emergence in patient A required two additional substitutions, an isoleucine change at residue 169 and a valine substitution at residue 250. Patient B needed glycine and isoleucine substitutions at residues 184 and 202 respectively, along with a subsequent change at residue 169. In both cases these changes occurred in the background of preexisting lamivudine-resistant substitutions. Both isolates were growth impaired and remained fully susceptible to adefovir.

The impact of substitutions at each of these four residues of entecavir's susceptibility are shown on this slide. Recombinant viruses containing the indicated substitutions at residues 169, 184 and 202 alone had no significant impact on entecavir's susceptibility relative to wild type virus, while a change at residue 250 reduced entecavir's susceptibility levels by less than 10-fold, about the same as when lamivudine-resistant substitutions alone are

present.

The 169 substitution appears to act as a secondary mutation and did not further reduce entecavir's susceptibility in the lamivudine-resistant viruses. However, when lamivudine-resistant substitutions are combined with the entecavir-resistant substitutions at residues 184, 202 and 250 significantly higher levels of entecavir resistance are observed. Presence of multiple entecavir-resistant substitutions further decreased entecavir's susceptibility levels.

An extensive resistance monitoring program was undertaken. In the nucleoside-naive trials all available entecavir-treated e-antigen positive and two-thirds of randomly selected e-antigen negative patients were genotyped at study entry and at week 48, a total of 550 pairs of patient samples. For the lamivudine-refractory population all available patient samples were genotyped. All emerging changes identified were tested for their potential impact on entecavir susceptibility.

In addition, samples from all patients experiencing a virologic rebound, defined as any greater than or equal to 1 log increase from nadir

identified by PCR, were genotyped and subjected to population phenotyping to determine if they harbored circulating viruses resistant to study drug. In nucleoside-naive patients treated with entecavir there was no evidence of genotypic or phenotypic resistance by week 48.

The figure plots the distribution of patients with the HBV DNA levels indicated at study entry and at week 48 for both entecavir and lamivudine. The size of each circle corresponds to the percentage of patients and each column of circles adds up to 100 percent. And, 81 percent of entecavir-treated patients achieved viral DNA levels of less than 300 copies/mL, represented by the bottom circle, compared to only 57 percent for lamivudine-treated patients. Overall, 88 percent of patients, represented by the bottom two circles in each case, achieved viral DNA reductions below 1,000 copies/mL on entecavir by week 48.

Genotyping identified 76 emerging changes but no distinctive patterns were observed, and no change was present in more than three isolates, representing 0.6 percent of those treated. Phenotypic analysis of these emerging changes show that their presence did not result in a significant

decrease in entecavir susceptibility. There were 11 virologic rebounds on the entecavir arms of these studies compared to 88 rebounds on lamivudine therapy.

This slide shows the origin and frequency of rebounds by study. When genotyped, nearly all of the observed virologic rebounds on lamivudine therapy coincided with the emergence of resistance substitutions at residues 180 and 204, yielding a confirmed resistance frequency of 8-18 percent by week 48. In contrast, none of the entecavir virologic rebounds observed in nucleoside-naive patients could be attributed to emergence of resistance.

A close examination of the individual patient profiles showed that all 11 patients

exhibiting a rebound on entecavir had at least a 3-log reduction in viral DNA levels and 7 of the 11 had greater than a 5-log reduction. Most importantly, all patients had viral populations that were full susceptible to entecavir at the time of rebound, and there was no evidence of emerging genotypic changes that reduced entecavir susceptibility.

From this comprehensive analysis we conclude that there was no evidence of emerging genotypic or phenotypic resistance to entecavir in any of the nucleoside-naive patients by week 48, a result that is most likely due to the high degree of sustained viral suppression observed. We continue to monitor these patients for resistance in subsequent treatment years.

Let us now turn to the lamivudine-refractory patient population where previous studies indicated that entecavir resistance emergence can occur. Similar to nucleoside-naive patients, entecavir was highly effective in lamivudine-refractory patients

enrolled in study 026 and in the 1 mg arm of study 014.

The figure again plots the distribution of lamivudine-refractory patients having the HBV DNA levels indicated at study entry, week 24 and week 48. While reductions were somewhat less than those observed in nucleoside-naive patients, 22 percent of entecavir-treated patients achieved viral DNA reductions below 300 copies/mL by week 48. There was a clear trend of sustained and increasing reductions from week 24 to week 48, and superiority to continued lamivudine therapy.

As part of our comprehensive resistance evaluation, all patients, regardless of treatment arm, were genotyped at study entry and week 48. There were 5 virologic rebounds among the lamivudine-refractory patients treated with entecavir.

The figure plots the HBV DNA levels for the first two patients, labeled 1 and 2. Both exhibited only modest reductions in HBV DNA levels on entecavir therapy. Evidence of entecavir

resistance substitutions at residue 184 were noted in both patients and population phenotypes indicated a 15-19-fold decrease in entecavir susceptibility, consistent with resistance emergence.

In contrast, the three other patients, labeled 3, 4 and 5, all experienced at least a 4-log reduction in viral DNA levels and further reductions following rebound either on continued therapy or off treatment, with no evidence of genotypic or phenotypic changes beyond those expected for lamivudine-resistant viruses.

Based on this evaluation, only two patients or one percent of lamivudine-refractory patients treated with entecavir experienced virologic rebound due to resistance by week 48. Entecavir-resistant substitutions were, however, noted in 12 entecavir-treated patients by week 48, all with a background of lamivudine-resistant substitutions. These patients continue to be monitored for virologic rebounds in subsequent years. Emerging substitutions at 14 other residues

were also identified, but none were present in more than 3 patients or reduced entecavir susceptibility beyond those expected for lamivudine-resistant viruses.

An unexpected finding was that lamivudine can preselect for entecavir-resistant substitutions. This was further supported by the observation that lamivudine-treated patients showed evidence of emerging changes at residues 169 and 184 in study 026. Among the greater than 360 lamivudine-refractory patients genotyped, at least 22 had detectable changes at entecavir-resistant substitutions at study entry. Nine were randomized to an entecavir treatment arm, where two progressed to have resistance-induced virologic rebounds described earlier. Only 2/9 patients were able to reduce viral DNA levels below 300 copies/mL. This observation, along with the other results described in this presentation, indicate that extended use of lamivudine will not only select for the primary lamivudine-resistant substitutions at 180 and 204, but can also select for a number of secondary

substitutions that can significantly reduce entecavir susceptibility and clinical efficacy.

This slide summarizes our current understanding of the entecavir resistance profile at week 48. There was no evidence of genotypic or phenotypic resistance in any studied nucleoside-naive patients treated with entecavir. Entecavir did not select for lamivudine-resistant, or entecavir-resistant substitutions, or other novel substitutions that result in decreased entecavir susceptibility and there were no virologic rebounds due to resistance.

Among the patients having primary lamivudine-resistant substitutions at residues 180 and 204, 7 percent exhibited emerging entecavir-resistant substitutions while on entecavir therapy, and only 1 percent of lamivudine-refractory patients exhibited a virologic rebound due to resistance by week 48. The preexistence of entecavir-resistant substitutions appears to be a marker for decreased efficacy and potential virologic rebound.

In summary, the potent and sustained suppression of viral replication by entecavir likely accounts for the absence of resistance

emergence in nucleoside-naive patients. An extensive analysis of nucleoside-naive patients showed no evidence or resistance. Entecavir was also effective in lamivudine-refractory patients where only 1 percent of patients experienced a virologic rebound due to resistance by week 48. Substitutions correlated with entecavir resistance were identified at primary residues 184, 202 and 250 and the secondary residue 169. Lamivudine-resistant substations are a prerequisite for achieving high level entecavir resistance and lamivudine treatment can preselect for some entecavir-resistant substitutions.

We conclude that this virologic profile provides critical information to physicians regarding the placement of entecavir in the armamentarium of drugs available to treat chronic hepatitis B infection. Dr. Donna Morgan Murray will now conclude our presentation with

pharmacovigilance and final summary.

Pharmacovigilance and Summary

DR. MORGAN MURRAY: As you have heard this morning, the entecavir clinical development program was extensive. It was the largest HBV program conducted to date and the only antiviral HBV program to use an active comparator in Phase III trials. That comparator was lamivudine, the only agent available at the time of initiation of the trials and the most common HBV therapy used to date.

Entecavir demonstrated substantial clinical benefit in Phase III and was superior to lamivudine in the prespecified primary endpoint of improved histology. Entecavir was also superior to lamivudine in most of the secondary endpoints.

Based on the rodent tumor findings, entecavir is a rodent carcinogen. The lung tumors appear to be species specific, and the other tumors occur at high exposure multiples. The investigative data submitted to the carcinogenicity assessment committee do not definitively eliminate

a risk for humans. With more than 2,300 patients treated with entecavir, there is no safety signal related to malignancy in the clinical development program. While this is reassuring, we recognize that the observation period is short.

As Dr. Sigal mentioned, we are committed to continuously assessing the benefit versus risk profile of entecavir, and have proposed a post-marketing pharmacovigilance plan with three main components. In addition to routine post-marketing surveillance, the pharmacovigilance plan also includes real-time monitoring of special events, specifically malignancies and hepatic events. We have designed special questionnaires to aid in collecting follow-up information for reports of both malignancies and hepatic events. We will periodically review post-marketing and clinical trial adverse event data, using quarterly aggregate frequency reports, and we will review these events of special interest.

There are three ongoing long-term safety studies and we have proposed an additional large,

prospective, randomized safety study to be conducted post-marketing. First let's review the ongoing studies.

The clinical development program included one- to two-year treatment studies and long-term safety studies with careful observation for the development of malignancies. Responders from the Phase II/III trials were encouraged to enroll in an observational study that was aimed to gather safety data off treatment. Malignancy was the primary focus of this observational study. Some patients from the Phase II treatment studies were eligible to enroll in open-label treatment studies, and these patients were also encouraged to enroll in the observational study.

To date, more than 80 percent of patients from Phase III have enrolled in at least one of the long-term safety studies, and the observational study has more than 400 patients enrolled, with the expectation that we will enroll up to 1,500 patients and all patients will be followed for 5 years. In addition to the ongoing studies, we

propose initiating a large safety study post approval.

Given the limitations of pre-approval clinical studies, we recognize that we cannot rule out a cancer risk in patients treated with entecavir. Pre-approval studies do not provide sufficient numbers of patients to rule out such uncommon events. We considered several options for further assessment and concluded that a randomized, prospective study would permit rigorous analysis of these events of special interest--mortality, neoplasms and progression of liver disease.

The draft protocol for this study calls for patients to be randomized 1:1 to entecavir versus another standard of care nucleoside or nucleotide; to be stratified as naive or previously treated; and to be followed for at least 5 years. It is our intent to engage an external, independent data safety monitoring board to conduct periodic reviews of the data from this study.

We propose to conduct the study globally and to recruit patients via their own physicians.

Patients who are starting a new HBV therapy or are changing their therapy will be eligible to enroll. We expect to enroll a total of 12,500 patients. We will report annually on rates of all-cause mortality, malignancy and progression of liver disease. While other common nucleosides also have rodent tumor findings, and the benefit-risk assessment was favorably concluded based on the serious nature of the disease, such as AZT for HIV, few have been the subject of the rigorous assessment that we propose here.

However, the proposed study does have several challenges. First, the planned primary analysis is intent-to-treat and, as patients will inevitably switch therapies over the course of the study, the primary analysis may be confounded. However, we will not limit our review of the data to this analysis and we will look at the data in several different ways.

Second, there may be limited ability to detect treatment group differences for events of variable latency. Since all patients will be

studied for at least 5 years, and many may well be studied for up to 8 years, we should detect a signal if there is an increased risk.

Third, the study is designed to detect differences in overall malignancy rates and in rates of HCC, but is not designed to detect treatment group differences for individual malignancy types.

Finally, attrition will occur but this does not mean that patients will be lost to follow-up. We will implement tactics to enhance follow-up, and we have developed strategies to address these challenges listed on this slide, and conclude that the proposed study will provide important data on both the benefits of entecavir and on further risk assessment.

Adequate data exist to demonstrate the substantial benefit of entecavir over existing therapies. Entecavir provides superior viral suppression in both nucleoside-naive and lamivudine-refractory patients. Specifically, treatment with entecavir resulted in up to a 7-log

decrease in HBV DNA.

Entecavir results in superior normalization of ALT in both nucleoside-naive and lamivudine-refractory patients. Up to 78 percent of patients achieve normal ALT.

Entecavir also provides superior improvement in histology in both nucleoside-naive and lamivudine-refractory patients. Treatment with entecavir resulted in up to 72 percent reduction in necroinflammation.

Entecavir has a favorable resistance profile compared to lamivudine. As you heard from Dr. Colonno, no resistance substitutions emerged in nucleoside-naive patients and resistance substitutions were uncommon in lamivudine-refractory patients.

Given the demonstrated superiority of entecavir in viral suppression, ALT normalization and improved histology, and the favorable resistance profile both in nucleoside-naive and lamivudine-refractory patient populations, long-term benefits of entecavir might include a

reduction in disease progression, such as lower rates of liver failure, liver cancer, liver transplant and liver-related deaths.

We conclude that the demonstrated benefits of entecavir represent an important treatment advance for HBV infection. The demonstrated benefits of entecavir against HBV, a known carcinogen, are indeed substantial and outweigh the theoretical risk posed by the rodent tumor data. Thank you for you attention this morning.

Questions from the Committee

DR. ENGLUND: Thank you very much, Dr. Murray. I would like to thank the Bristol-Myers Squibb people for a very clear, concise and timely presentation. It was very nice. Thank you.

This is the time that we are going to open up for questions to the panel, but I would like to caution people that the questions are supposed to be directly related to the information presented today. We will have discussion time later on but if there are clarifications or questions about specific points related to the presentation we just

heard, now is the time to begin so I will open it to the panel for questions. Dr. DeGruttola?

DR. DEGRUTTOLA: Yes, I have two questions. The presentations mentioned that the studies in dogs and rats did not find an increased risk of lung cancer associated with entecavir. I was wondering how long those studies had gone on; were they powered to be able to detect such an effect? Then, regarding the post-marketing study to try to determine an effect on cancer in humans, I was wondering what the power will be in that study; what magnitudes of effects is the study powered to detect?

DR. MORGAN MURRAY: First I will ask Dr. Lois Lehman-McKeeman to address your first question about the duration of studies in dogs and rats.

DR. LEHMAN-MCKEEMAN: I will speak to the rats first because they were, in fact, one of the species used in the lifetime carcinogenicity study. So, in two years, for the lifetime of the rat, there were no tumors in the lung that developed.

The dog the studies were not conducted to

be carcinogenicity studies; they were chronic toxicology studies and they were three months in duration. However, what we understand about the lung lesion in the mouse is that it develops very quickly and the early preneoplastic change that I described occurs within the first two weeks of dosing. In the course of a three-month study in dogs we saw no early preneoplastic change.

DR. DEGRUTTOLA: Thank you.

DR. MORGAN MURRAY: And for your second question about the power of our post-marketing study to detect differences, Dr. Phil Pierce will address that.

DR. PIERCE: The primary goal of the large safety trial is to investigate the potential treatment effect on the development of non-HCC malignancies. First we had to establish what the background rate in this population is, and we utilized the data from the Taiwan cohort that was presented, as well as the background rates that we saw in the BMS studies.

The background rate was approximately 4

non-HCC cancers over 1,000 patient-years of follow-up. We estimated from that that there would be 16 non-HCC malignant events per 1,000 patient-years per arm over 5 years. Also, the total accrual of time will be 65,000 patient-years. Our study was designed to show a 30 percent increased risk of malignancy. That translates into 5 additional cancers per 1,000 patient-years over the 16 that I mentioned earlier. I believe BMS concludes this is a reasonable assessment of that risk.

Slide 1-520, please. I gave you a lot of numbers with that and I want to show the expected events in the untreated population over the 5 years. The rate that I mentioned for the non-skin, non-HCC cancers is 16 as the expected rate and we would have a power to detect, with this sized population, an increase of 5 over that 16. The additional benefit of this study is that we will also be able to analyze the impact on the other events of interest which, obviously because of the large size of those, we are adequately powered to

show whether we have an impact on the rates of HCC and on the progression to cirrhosis.

DR. DEGRUTTOLA: Thank you.

DR. ENGLUND: Thank you. Dr. Washburn?

DR. WASHBURN: It is very interesting that the study drug is chemotactic for mouse monocytes but not human monocytes. I wonder if there is any work that can be shared that would discuss some mechanism of that difference. Does it relate to complement activation, or a macrophage chemotactic peptide, or other? The question is of potential relevance in the carcinogenicity of disease.

DR. MORGAN MURRAY: Dr. Lehman-McKeeman will address that.

DR. LEHMAN-MCKEEMAN: At this point in time we don't know the molecular basis of that difference. What we know is that based on the fact that macrophages were accumulating in the lung and were not proliferating to accumulate, we looked specifically for a chemotactic event and we tested that in some standard in vitro systems. When we did that work, there is clear chemotactic activity

to the mouse with no effect in the human at all.

Now, to go further, we have looked, in doing some investigative work, at whether or not altering macrophage recruitment alters the progression of this lesion. To do that, we have looked at a CCR2 knockout, so chemokine receptor to a knockout animal, and we found that that mouse does, indeed, have a very different response to the drug. It is no unequivocal proof that this is mediated through CCR2, but it suggests that it plays a role.

I want to add one other factor though, and that is that the lesion that we see involves accumulation of macrophages but, based on our assessment, those macrophages don't appear to be activated. They are simply accumulating.

DR. WASHBURN: Thank you.

DR. ENGLUND: Dr. Fish?

DR. FISH: I didn't hear my name earlier in the disclosure statement and I just need to add that though I signed the disclosure waiver, I have been on the speakers bureau for the sponsor and two

competitors.

The question that I have is on the study were there pregnancies and, if so, the outcomes of those pregnancies in entecavir-treated patients?

DR. MORGAN MURRAY: I am going to try out Dr. Brett-Smith's voice here. So, Helena?

DR. BRETT-SMITH: The studies were designed that if pregnancy was determined to occur during the course of the study the patient was to immediately stop study drug. Indeed, pregnancies do occur. The majority of these actually resulted in elective termination of pregnancies.

If we could show slide 5-79, this includes the various treatment combinations that have been used across our entire program to date with entecavir alone, lamivudine alone, entecavir in combination with lamivudine, for the initial period of the 901 long-term rollover study and also in placebo.

As you can see, the majority of pregnancies identified resulted in elective termination. There was a small number of

spontaneous abortions. There have been 6 live births. The 4 outcomes that are listed as "unknown" are progressions that are currently under way and for which we are actively pursuing follow-up on those deliveries.

With respect to the live births, across those live births there were no reported defects in 5 out of the 6 cases. There was, indeed, 1 live birth where the mother had received entecavir 0.5 mg for a total of 44 weeks but the diagnosis of the pregnancy was made at approximately week 7 of gestation. That had a fairly complicated history. The child was born with what has been reported to us as a severe cerebral cortex defect. Unfortunately, despite repeated contact with the site, the family has not wished to provide us with further data.

The details of the early pregnancy are a little complex so let me walk you through those. The patient had discontinued entecavir immediately at the time that pregnancy was diagnosed, as I said, about week 7. The patient then experienced

what was clinically diagnosed as a spontaneous abortion and was told by the gynecologist that no fetus had been present. A subsequent ultrasound actually did reveal a live fetus, but in the interim entecavir had been briefly restarted by the clinician for 2 weeks and the moment the ultrasound became available it was discontinued. So, that represents the sum of our experience to date in the program with pregnancy.

DR. ENGLUND: Dr. Haubrich?

DR. HAUBRICH: It is clear that emergence of viral resistance to therapy is dependent on the degree of viral suppression and, clearly, drugs that have greater suppression will have less emergence of resistance. It is also clear from extensive experience in AZT that after 15-20 years of nucleoside therapy we are still identifying new mutations. So, perhaps I didn't follow it well, but if you could clarify the emergence of mutations that may have occurred with entecavir. Although they may not lead to phenotypic susceptibility since the number of mutations is few at this point,

you know, they may in the future be defined when greater numbers of samples are available.

So, just a comment that it is clear that the resistance profile is better with greater suppression, but it seems a little premature to be saying that there is no resistance that develops on therapy when the number of specimens is low and it may be a bit early. So, if you could comment on that I would appreciate it.

DR. MORGAN MURRAY: I will ask Dr. Colonno to comment but first I would like to note that the original NDA and the safety update--at that time we only had 48-week data available and that is the only data that have been submitted for review. But very recently we did complete the analysis on patients who have been treated for two years and Dr. Colonno can perhaps share those data as well.

DR. COLONNO: Let me just deal with the first part first in terms of the number of mutations, just to give you a sense of what mutations were found.

Can I have slide 1-315, please? This is a

list of all the mutations that have been found or identified in all patients examined that have taken entecavir--as you can see, a very wide range. The vast, vast majority of these, again, have occurred at polymorphic sites. We call them new emerging substitutions because they have not been described previously at those particular sites.

Again, I will point out that these mutations do not occur in any more than three patients. Most of these occur in a single patient, again, representing less than one percent. We have tested all of these different mutations and substitutions not only by themselves but also in the context of their preexisting clinical background and, as you can see by the EC 50s that are present, they really do not alter the normal wild type susceptibility.

Now if I can just move to your statement, which I think is a correct one and, again, as a virologist having worked in resistance for many, many years, there is no such thing as no resistance. So, we have gone out to the second

year, and this is real-time data and the data continues to come in, and I would like to just share with you some very encouraging data for the second year.

This is the second year data as it currently stands. On the left-hand side, again, are the bubble charts and the first thing I want to point out is this is study 022 where we have the most data. You can see that the continued progression in decreasing DNA from week 48 to 96, where we have 65 undetectable now, we continue to drive viral load down with 81 percent of patients now with undetectable virus.

That correlates with the table on the right where, again, despite the fact that we have treated now for 2 years, we have a very similar profile to what we saw in year 1. In year 2 we have a total of 7 rebounds, virologic rebounds using the definition I described earlier but, again, looking at their genotypes and phenotypes we see no evidence of any genotypic or phenotypic resistance. So, out to 2 years in the

nucleoside-naive population with that type of viral suppression we have not observed any resistance to entecavir.

DR. ENGLUND: Dr. Johnson, do you have a specific question about that?

DR. JOHNSON: Victoria Johnson, University of Alabama at Birmingham. As a virologist and viral resistance person, I share concerns that despite the elegant data presented, given this compound's potency, as you realize, two years may not be enough, and I want to just ask is this part of the pharmacovigilance monitoring plan? That is one question.

The second question is, if you can go to your second to last slide of your previous presentation--

DR. MORGAN MURRAY: Let me answer your first question first around the pharmacovigilance plan. Several of our studies are ongoing, as I had mentioned, and in all of the ongoing clinical studies we do continue to monitor for resistance. Acknowledging that the pharmacovigilance plan is

very large, we will have many centers and it will be usual practice, we feel it will be impossible for us to get resistance data on all of the 12,500 patients. But what we do propose is to have a sub-study, a subset of patients, a center in the U.S., a center, you know, here and there that we will get much more data including resistance data. I will let Dr. Colonno address your second point.

DR. COLONNO: We will continue to look for resistance until we find it. Again, there is always going to be resistance at some point. But the key point of this slide, which we don't have with HIV, unfortunately, even with combination therapy, is the ability to drive viral load down by 6 or 7 logs, 8 logs in some cases and to maintain that for a very long period of time. Those viruses require a minimal amount of replication to give rise to resistance. So, we are encouraged. Again, that is not to say there will never be resistance but we are highly encouraged with that kind of suppression and with the limited ability of the virus to actually replicate that a large amount of

resistance will all of a sudden come up. We will continue to monitor these patients for the foreseeable future.

Another interesting point is that these particular patients do not give rise to any evidence of resistance substitutions being selected. We know lamivudine resistance is a stepping stone to becoming clinically relevant resistance to entecavir. But the fact that we, again in that population, see none of those changes really coming up again is encouraging but, again, it is only two-year data for a large number of patients, but not a tremendous amount, so we will continue to monitor in subsequent years.

DR. JOHNSON: My second question is on your second to last slide, just for clarification.

DR. COLONNO: My second to last slide?

DR. JOHNSON: Yes, from your earlier presentation. It was called summary of viral resistance data at week 48. So, just to clarify, and I think part of this got answered, the title is week 48 but the bottom data are presented on two

patients who had greater than 76 weeks.

DR. COLONNO: Those two patients were from the Phase II study. They are not included here; they were Phase II.

DR. JOHNSON: So, they are different than the two on this slide that are on the bottom?

DR. COLONNO: These two are from the Phase III evaluation.

DR. JOHNSON: At week 48?

DR. COLONNO: At week 48.

DR. JOHNSON: And that is different than the other two patients you described with virologic rebound resistance?

DR. COLONNO: That is correct. One was in the 015 study which was a transplant study, and the other one was in 014.

DR. JOHNSON: But they appear to select the same signature mutations?

DR. COLONNO: They select the same signature mutations. Those three mutations appear to be the key primary resistance markers for entecavir.

DR. ENGLUND: Dr. Sherman?

DR. SHERMAN: The presentation indicated that phosphorylation was required for this product.

Could you comment on any data you have regarding interactions with anti-retrovirals that also require phosphorylation in vitro? I know you have limited in vivo HIV-positive patients, but is there any pharmacokinetic analysis and any issues of changes in resistance to HIV or susceptibility because of the interaction?

DR. MORGAN MURRAY: I will let Dr. Colonno follow up on that.

DR. COLONNO: We have done an extensive analysis of the interactions because it is a nucleoside analog and there are many nucleoside analogs that are used in HIV, interactions based on the phosphorylation patterns of these various combinations. What I can tell you is that because the concentration of entecavir is so low relative to other nucleoside analogs and the efficiency is so high, when one does in vitro cell culture combination studies to look for the effect of

entecavir on the antiviral potency of the HIV nucleoside analogs, or in the opposite direction in the presence of the HIV and RTIs and does it have an impact on entecavir activity, we find, using concentrations of both sets of compounds up to five times their C max, clinical Cmax, we see no interactions whatsoever; no antagonism; and no decrease in the activity. Again, that is a big plus for entecavir because entecavir is very selective for hepatitis B and so it literally also can be used in a co-infected patient but not having to worry about any kind of selective pressure on HIV.

DR. ENGLUND: I am going by the order that I saw the hands come up, which may be wrong, and we are only going to have time for about four or five more questions. But the first question was Mr. Grodeck's.

MR. GRODECK: In terms of marketing antivirals, one of the biggest games I have seen pharmaceutical companies play is the sequencing game--my drug should come before your drug. In

your description of the resistance profile of entecavir, it seems to me that you are setting up the drug to be positioned as a first-line treatment. Is that your position? How does it fit in terms of the range of other treatments available to chronic hepatitis B patients today?

DR. MORGAN MURRAY: I will ask Dr. Dienstag to comment on how entecavir might fit into current treatment guidelines and the physicians' armamentarium. I will just remind you, from our data, that we have demonstrated that entecavir is superior to lamivudine. We have substantial benefits in both nucleoside-naive and lamivudine-refractory patients.

DR. DIENSTAG: Jules Dienstag, Massachusetts General Hospital. I think if we consider hepatitis B a viral disease, then the drug that suppresses HBV most profoundly is likely to have the most benefit. That has been shown in this study for histology, biochemical markers and especially for the profundity of suppression of HBV DNA. In almost 90 percent of patients you can

achieve an undetectable level of HBV DNA, which no other antiviral comes close to at this point.

So, it is not unreasonable to suggest that this would be a first-line therapy. When you add the resistance profile and when you consider the potential that, for example, a drug like lamivudine sets you up for lamivudine resistance in the future and also sets you up for resistance to any other nucleoside, it makes sense to start with this drug. It is a very reasonable suggestion.

DR. ENGLUND: Dr. Paxton, did you get your question answered?

DR. PAXTON: Yes, it was. Thank you.

DR. ENGLUND: Dr. Wood, or were you first, Dr. Seeff or Dr. Schwarz?

DR. SCHWARZ: I have two questions relative to future applications of entecavir. You said that in the animal carcinogenicity models in the organ involved with the tumor there were ETV-induced dNTP pool perturbations. In either the animal studies or in the human studies, was there evidence of peripheral blood lymphocytes--the same

phenomenon occurring in peripheral blood lymphocytes that might be a useful non-invasive surrogate marker for malignant potential?

Then the second question is I assume in these lifetime exposure studies that the drug was not started in the immediate newborn period. So, at what age of the animal was it started, and can you make an educated guess about the human equivalent age?

DR. MORGAN MURRAY: I will ask Dr. Lehman-McKeeman to address the data that we have in animals around dNTP pool perturbations and also about the rodent studies. I will just comment that we do not have any human data around dNTP pool perturbations. As Dr. Lehman-McKeeman will describe, these perturbations in animals occur at much higher doses than we administer in humans.

DR. LEHMAN-MCKEEMAN: I will actually address the second question first for you. The studies that are conducted in rodents basically start when they are approximately 5-6 weeks of age. For perspective, that is when a rodent reaches

sexual maturity. So, in a 2-year life span, if I had to extrapolate, I will just say at sexual maturity so it would be roughly teenage.

To your first question about the dNTP pools, in the work that we did we specifically looked at target organ effects related to carcinogenicity. So, we specifically looked at the liver and we don't have any data on another system. Those analyses are actually quite, I will say, difficult to do, as it were, simply because the pools themselves are really quite fleeting. So, it really is prohibitive for us to collect more then one sample and we targeted the liver. However, what we know, based on the work we have done, is that that is a high dose phenomenon. So, at dosages where we saw carcinogenic activity we saw perturbations in pools, and at a dose below a carcinogenic effect we did not seriously disrupt pools. So, I think it is a function, again, of the maximum tolerated dosage that we are administering in the carcinogenicity studies.

DR. ENGLUND: Dr. Wood?

DR. WOOD: My question has to do with analysis of rates of malignant neoplasms according to ethnicity. This is related to the fact that I

believe I read that Asians have a higher pharmacokinetic exposure to entecavir and I was wondering whether or not an analysis had been done on that basis.

DR. MORGAN MURRAY: I will ask Dr. Brett-Smith to come up again. I will try and spare her voice a bit and comment that while we have not seen PK differences on the basis of race in particular, the differences that we do detect are related to weight more than to race. Dr. Brett-Smith, on the malignancies?

DR. BRETT-SMITH: At this point we have chosen not to look at any subpopulations in terms of the overall rates in malignancies because the total numbers remain low, and we believe that the rates would be sort of unreliably variable. That may become an option later in terms of the pharmacovigilance.

DR. ENGLUND: Dr. Seeff?

DR. SEEFF: I thought that the efficacy data that were presented were fairly impressive but there are a couple of questions that I just need some clarification on. Perhaps you presented them and I missed them.

The primary endpoint for your study was

histologic using the Knodell score. I gather that this is not unusual; this is fairly routine. Is this the 18-point HAI score?

DR. MORGAN MURRAY: Yes.

DR. SEEFF: In other words, the drop for example from 10 points to 8 points would represent an endpoint having been achieved.

DR. MORGAN MURRAY: Correct.

DR. SEEFF: What was the average drop? Do you know what the average decline in points was, just to get a sense of how much improvement there was in histology? Do you have those data by any chance? I mean, you have the percentage of people who achieved a 2-point reduction, but what I am interested in knowing is by how much of a reduction.

DR. MORGAN MURRAY: Dr. Brett-Smith?

DR. BRETT-SMITH: Yes, we do have data and I can present it for you if we can show slide 2-66. Overall, in the naive patients it was approximately a 4-point drop in the mean score, and in the refractory patients it was approximately a 3-point drop.

DR. SEEF: That is fine. Thank you. The second thing is your secondary endpoints,

essentially a reduction in HBV viral load and normalization of ALT, do you have a composite score taking into account the virologic, histologic, biochemical reduction? Do we have a score of using those three parameters?

DR. MORGAN MURRAY: Dr. Brett-Smith?

DR. SEEFF: And is it the same between entecavir and lamivudine for example?

DR. BRETT-SMITH: If I can just repeat the factors that you are interested in, you are interested in combining histology with virology--

DR. SEEFF: And with biochemical response.

DR. BRETT-SMITH: With ALT.

DR. SEEF: ALT.

DR. BRETT-SMITH: Those three. We have looked at a number of ways of combining virology with ALT. I will ask my colleagues to confirm whether we have yet completed the analysis combining with histology. I do not have that at this time.

DR. MORGAN MURRAY: So, we will confer during the break and see if we can quickly pull something together to answer that.

DR. ENGLUND: Last question, Dr. So?

DR. SO: There is a common belief by many

clinicians that, you know, if you have e-antigen seroconversion you pretty much, you know, have a good response and you might be cured. So, I notice that earlier in this handout to us, the committee members, you did describe some follow-up on the patients in your study 22 where they have so-called complete response. Some of the patients were taken off drugs. Do you have two-year follow-up information regarding how many of those patients have so-called sustained response and what

sustained response means?

DR. MORGAN MURRAY: I will ask Dr. Brett-Smith to comment, and I need to make the statement that in the NDA and the NDA update we only had the 48-week data so, again, these data have not been submitted for review.

DR. BRETT-SMITH: I heard a two-part question there. Let me just clarify. I heard first for patients who, at the end of year one, went off dosing--you were interested in the sustained response off treatment.

DR. SO: Right.

DR. BRETT-SMITH: Also, did I hear an interest in what happens to the portion of partial responders who have a virologic response--

DR. SO: No, I am just interested in your so-called complete responders.

DR. BRETT-SMITH: Let me first summarize for you the design of the studies at the week 52 endpoint. A clinical decision was made based on laboratory results from week 48 as to the management of the patient, which was simply a

management algorithm that was modeled on guidance at the time and it differs for each population. In the e-antigen positive population we required, in order to go off therapy, that patients have lost e-antigen and have an HBV DNA less than the bDNA assay level of detection, so less than 0.7. In the e-negative population patients had to meet the virologic requirement of bDNA less than LOQ, and they had to have an ALT less than 1.25 times the upper limit of normal. In the refractory antigen positive patients we again required that the patients achieve the virologic endpoint in association with e-loss. In that last group there were very small numbers of patients going off treatment, therefore, we will not discuss that further; the numbers were substantially small.

With respect to the two naive patient populations, if we could show slide 2-380, the studies were designed to follow people out to 24 weeks of off-treatment follow-up. If during that time patients went on alternative therapy or into the rollover study they were considered failures to

maintain that endpoint. These represent the respective percentages in the naive e-antigen positives on the left, 82 percent for entecavir and 73 percent for lamivudine, who maintained their study-defined response rate at week 24 off treatment. Likewise, in the naive e-antigen negative population we had 48 percent for entecavir and 35 percent for lamivudine.

DR. SO: But I don't think you answered my question. How many of those patients who were off treatment actually were followed up, like actually 48 weeks off treatment, are still off treatment? You know, it could be very misleading for a lot of clinicians when you say sustained response, not knowing, you know, for how many of those patients actually their histologic improvement was sustained? Was the virologic improvement sustained at 48 weeks? So, I feel that the 24-week off treatment, so-called sustained response, could be misleading.

DR. BRETT-SMITH: Point taken, 24 weeks is what had been agreed upon with regulatory

authorities in the design of the original study. All patients are encouraged to enroll on completion of the original study in the 049 long-term rollover study which remains currently enrolling at this time and has not undergone its initial analysis.

DR. SO: Just one last question, how does your company plan to talk to those clinicians who say, you know, if my patient seroconverted--these are naive patients before treatment, if they seroconverted I am planning to stop the treatment? How do you plan to advise those clinicians?

DR. MORGAN MURRAY: Our current proposed labeling reflects how the studies were conducted, and in that regard, for those patients who were determined to be responders therapy was stopped at 48 weeks and they were monitored. Patients who were partial responders continued on therapy. Our current trials cannot define the definitive duration of dosing for entecavir, which is in general in flux for HBV therapy. Dr. Dienstag, do you have any further comments?

DR. DIENSTAG: Jules Dienstag, Mass.

General Hospital. No one really knows what the sustained responsiveness or the durability of an e-antigen response is, but in the experience we have for interferon, lamivudine and adefovir if a person maintains that serologic response for 6 months after stopping therapy the durability is 80 percent. That is the experience in Asia and in the West. I assume that that will be repeated in this experience but that remains to be seen.

DR. ENGLUND: Thank you, everyone, for asking questions, answering questions. We will now take a 15-minute break. We will be back at 10:25 to resume the FDA portion of this morning's presentation.

[Brief recess]

DR. ENGLUND: Thank you. Welcome back from coffee. We are now going to have an FDA presentation led by Dr. James Farrelly, the pharmacology team leader, and he will begin his presentation.

FDA Presentation

Carcinogenicity Issues

DR. FARRELLY: Good morning. My name is Jim Farrelly. I am the pharmacology team leader in the Division of Antiviral Drugs.

Today our purpose is to present some of the data relating to the genetic toxicity and the animal carcinogenicity of entecavir. Entecavir is a nucleoside analog and, as such, is a member of a class of molecules which are in general expected to be genetically toxic. Its 5-prime hydroxyl can be phosphorylated to the nucleotide triphosphate and as a guanosine triphosphate analog can be incorporated into the growing DNA chain. It has the three-prime hydroxyl group and is, therefore, not an obligate chain terminator as are many other nucleoside analogs.

However, after incorporation of entecavir into the growing DNA chain, it halts DNA synthesis after the addition of a small number of subsequent bases. Its mechanism of action is essentially as a chain terminator, which is consistent with its being a clastogenic compound or having the ability to break chromosomes. Indeed, entecavir has been

shown to be clastogenic in an in vitro assay in human lymphocytes.

It is negative in a number of genetic toxicity tests both in vitro and in vivo. These include an Ames test, an in vitro assay in Chinese hamster ovary cells, in the Syrian hamster embryo cell transformation assay, and in an in vivo rat micronucleus assay, and in an unscheduled DNA synthesis assay. In general, most of the battery of genotoxicity tests can be used only for hazard identification. They are not used for risk assessment but have indicated that entecavir can be a possible genetic toxicity hazard.

In an effort to place the results of the genetic toxicity studies into perspective, one can compare the outcome of the studies used to evaluate entecavir with the outcome of the studies used to evaluate the genetic toxicity of the three entities approved for the treatment of hepatitis B. The three are adefovir, lamivudine and interferon.

Adefovir is a nucleotide analog rather than a nucleoside analog, and was found to be

mutagenic and to induce chromosomal aberrations in two in vitro genetic toxicology studies. Lamivudine, or 3GC, is a nucleoside analog and was found to be mutagenic in two in vitro assays as well. Interferon was not an active genetic toxin. Since it is a protein one would not expect interferon to be positive in the screening battery used to test for genetic toxicity. However, most of the nucleoside analogs approved as antiviral antigens are positive in genetic toxicology batteries of tests.

Now, as is usual for a drug that is going to be administered chronically to humans, entecavir was evaluated in two-year carcinogenicity studies in rats and mice. The design and outcome of the study in rats can be seen in the next slide where the data for male rats are shown.

Entecavir was administered by gavage to rats at four doses, 0.003, 0.02, 0.2 and 1.4 mg/kg/day. They were administered for 96 weeks. There were two identical vehicle controls in the study. The doses in male rats represent the human

equivalent exposure of much less than 1, 0.3, 5 and 35 times the clinical dose at the 1 mg proposed clinical dose, which you see under MHD.

In male rats at an exposure 35-fold that in the clinic entecavir caused the appearance of a low level but significant incidence of brain gliomas. A no-level of tumors was seen, or very low level, at 5-fold the exposure, and below no significant number of tumors was seen in the study.

The next slide shows the results in female rats. As can be seen from this slide, entecavir was administered at doses of 0.01, 0.06, 0.4 or 2.6 mg/kg/day for two years. Dosing was again by gavage and drug groups as well as two identical vehicle control groups were treated for 104 weeks. As can be seen in the slide, entecavir again induced the appearance of brain gliomas at the high dose. It also induced the appearance of skin fibromas at the high dose, and increased the incidence of liver tumors at the high dose from 1-8 adenomas and from 0-3 carcinomas. The exposure to entecavir at the high dose in which these tumors

were seen was approximately 24-fold higher for females than that measured in the clinic at the 1 mg dose.

Mention should be made regarding the exposure multiples at which tumors were seen in the study. Although a multiple of 24 in exposure is a high multiple of the human exposure, it should be remembered that there were no significant induction or increase in tumors at the 4-fold for females and 5-fold level for males. The real cutoff, therefore, is somewhere between the high dose and the next lower dose, and the no-observed effect for tumors was at the 4- and 5-fold human dose.

The results of the mouse carcinogenicity study were more complicated. In the next slide it is shown that male mice were treated in a similar manner as were the rats. The doses of entecavir used actually in both the males and the females were the same on a milligram per kilogram per day basis. The doses were 0.004, 0.04, 0.4 and 4 mg/kg/day.

As seen here, entecavir caused a

dose-related increase in common bronchoalveolar adenomas in the males, significant at the three higher doses. The lowest of the three doses produced an exposure only 3-fold higher than the clinical exposure. Also increased in the males was the incidence of hepatocellular carcinoma at the high dose, going from 1 in one of the controls to 8 at the high dose. The exposure in the latter case was 42-fold higher than the clinical exposure. For the hepatocellular carcinomas no increase was seen at an exposure 40-fold the clinical dose, very low; not significant.

The next slide shows the female mice in which entecavir induced a significant increase in the lung tumors only at the high dose, giving an exposure in the animal study 40-fold the exposure in the clinic. There was no significant increase at 11-fold the exposure. Also in female mice there was an increase in ovarian and uterine vascular tumors, again at the high dose. If one combined all the vascular tumors, as is commonly done, there was a significant increase in combined hemangiomas

and hemangiosarcomas at the high dose.

We have heard the sponsor make a good case for the proposition that the pulmonary tumors seen in the mouse are mouse specific. No cellular proliferation was seen in the lungs of rats and no lung tumors in rats, as well as no cellular proliferation in the dog and monkey studies. If, indeed, the tumors were mouse specific the outcome would be that the only tumors seen in the two studies were at the high dose only.

Again, putting the results of the carcinogenicity studies into perspective with the other approved regimens for hepatitis B, no carcinogenicity studies were carried out with interferon. Studies were carried out with adefovir and lamivudine; they were not carcinogenic. However, because of kidney toxicity in the carcinogenicity studies, the exposures of the animals in the adefovir studies relative to the clinical exposures were 10-fold for mice and 4-fold for rats. The maximum tolerated dose cannot go any higher than those. So, if entecavir was examined

only at those exposures, it would have been positive only for the lung tumors in mice and for no other tumor types.

The exposures in lamivudine studies were high relative to the exposures in the clinic, up to 34-fold in the mice and 200-fold in the rats. At those exposures the entecavir results would have been at least identical to those which we have seen in these studies. However, many nucleoside analogs approved as antivirals have been positive in carcinogenicity studies.

The results of the two carcinogenicity studies were presented to the CDER Executive Carcinogenicity Assessment Committee, which we call the executive CAC, as well as to the full CAC for evaluation. The CDER CAC committees were formed in the late 1980s to examine the protocols of carcinogenicity studies, as well as to examine the outcomes of the same studies. The committees were founded so that the interpretation of the carcinogenicity data would not be inconsistent depending on which division reviewed them. Two

committees exist, the executive CAC, as I said, and the full CAC.

The executive CAC consists of four members, the associate director for pharmacology/toxicology in the center; one permanent expert in the evaluation of carcinogenicity studies; the supervisor whose division is presenting the data; and another supervisor from another division chosen on a rotating roster. The executive CAC meets every Tuesday and evaluates a great number of protocols and studies in a year, usually somewhere between 150 and 200 either protocols or carcinogenicity studies in a year.

The next slide shows the makeup of the full CAC which is empowered to review the studies when members of the executive CAC cannot unanimously agree on the interpretation of the data, or when requested by the sponsor of the drug. The full CAC consists of the associate director for the center; three associate directors for the offices; and each of the supervisors from the

individual divisions in the center. The full CAC is a fairly large committee and meets only rarely. In fact, the meeting for this drug was the first one in over a year for the full CAC.

Both the executive CAC and the full CAC agreed that the tumors seen in the studies were probably relevant to a safety evaluation for humans. The full CAC in general voted that the tumors seen in the carcinogenicity studies were relevant to human safety evaluation.

The questions asked of the committee were does the CAC agree that the lung tumors in mice were relevant to human safety evaluation? The committee voted yes, 16; no/probably not, 2; and 2 answered they don't know.

Does the CAC agree that, one, the liver tumors in male mice and, two, the vascular tumors in female mice are relevant to human safety evaluation? The vote was 17 yes; 3 no.

Does the CAC agree that, one, hepatocellular adenomas and carcinomas in female rats, two, the skin fibromas in female rats and,

three, the brain gliomas in male and female rats are relevant to human safety evaluation? The answer was yes, 17; 3 no.

Now, in our division many carcinogenic nucleoside and nucleotide analogs have been approved for the treatment of viral diseases. Among these are ganciclovir which gives rodent tumors at very low doses relative to the human exposure; zidovudine; abacavir and cidofovir. Cidofovir causes palpable mammary adenocarcinomas in rats after as few as six weekly doses and is closely related in chemical structure to adefovir. Some of the reverse transcriptase inhibitors as well as the HIV protease inhibitors are positive for animal carcinogenicity. Other drugs, such as 8-methoxy psoralen, which has been approved for the treatment of psoriasis, are carcinogens. In fact, this compound has been identified as a human carcinogen in epidemiology studies. Dr. Linda Lewis will continue the division presentation. Thank you.

Clinical Issues

DR. LEWIS: Good morning. My name is Linda Lewis, and I was the lead clinical reviewer for the entecavir review team. I would like to

give you the perspectives of the entire team on our review of entecavir for the treatment of chronic hepatitis B.

My presentation is outlined in this slide. First I will go over a little bit of the development program for entecavir, which you have heard presented earlier by Bristol-Myers Squibb. Then I would like to go over the results of our reviews of the efficacy, safety and virology/resistance data that were contained in the NDA submission. At that point I will turn my discussion to an assessment of the risk-benefit of entecavir and the applicant's proposed pharmacovigilance plan. I will end the presentation with a preview of the questions that we would like the advisory committee to consider later this afternoon.

As you heard this morning, the treatment options for chronic hepatitis B are somewhat

limited. Interferon was approved for treatment of hepatitis B in 1992. Its requirement for parenteral administration and its significant side effect profile have somewhat limited its use. Lamivudine was the first effective oral therapy, and it was approved in 1998. Its usefulness has been limited by the predictable emergence of resistance in relatively short periods of time. A most recent addition, adefovir, was approved in 2002. It has known renal toxicity that may limit its use in some populations.

The entecavir development program included a diverse patient population. The clinical studies were drawn from multinational sites in North and South America, Europe and Asia. Among these studies, patients from the United States made up about 10 percent of the pivotal trials. The entecavir studies were made up of about 20 percent women. There was a good mix of Asian and non-Asian patients in the populations. However, Black or African American patients were under-represented in the clinical trials, making up only 2 percent of

the pivotal studies. The development program enrolled patients at different stages of disease and treatment. Although there is a study in progress, the data were insufficient to review the use of entecavir in patients with decompensated liver disease during this review cycle.

BMS submitted study reports and electronic data sets for the four key studies that they have mentioned in their presentation earlier. To go over these again, study 022 was the Phase III study enrolling nucleoside-naive, e-antigen positive adults. Study 027 enrolled nucleoside-naive e-antigen negative adults. Both of these studies used a dose of 0.5 mg of entecavir given once daily. Study 026 enrolled patients with persistent HBV viremia despite lamivudine treatment. These are termed lamivudine-refractory subjects. Patients in this study were e-antigen positive and received a dose of 1 mg of entecavir given once daily.

In order to expand the safety database for lamivudine-refractory patients we included in our

review patients from study 014, the dose-finding study in that patient population, and used the cohorts that received either 1 mg of entecavir or the standard dose of lamivudine. As has been pointed out, all of the pivotal trials were compared to the standard dose of currently approved lamivudine.

For all of the Phase III studies, studies 022, 027 and 026, the primary endpoint was the overall histologic improvement in liver biopsy after 48 weeks of treatment. This histologic improvement was defined as greater than or equal to a 2-point decrease in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score compared to the baseline biopsy. A series of secondary endpoints were also evaluated and included a number of virologic, serologic, biochemical and composite endpoints.

The applicant also submitted data from several important studies in special populations. These included study 015. This was a small pilot trial in post-liver transplant patients who had

recurrent hepatitis B. Study 038 enrolled a cohort of HIV/HBV co-infected patients. Study 048 compares the use of entecavir to adefovir in patients we decompensated liver disease. This study is still enrolling and the data were not sufficient for us to conduct any meaningful interim analysis during this review cycle. In these studies histologic endpoints were not used. They relied on a series of virologic, serologic and biochemical endpoints.

Now I would like to turn to the efficacy review of entecavir. You will probably notice in these slides that many of our slides look very similar to those presented by the applicant earlier this morning.

The FDA statistical review, conducted by Dr. Tom Hammerstron, confirmed the applicant's primary efficacy analysis. A review of secondary efficacy analyses, using the virologic, serologic and biochemical endpoints, was also in agreement with BMS's conclusions. Multiple sensitivity analyses and subgroup analyses were performed and

all supported the primary analysis.

This table displays the results of the primary efficacy analysis and some of the other histologic endpoints for each of the Phase III studies, study 022, 027 and 026. The top line of the study shows the primary analysis, the overall histologic improvement after 48 weeks. As you can see, in each of the three studies entecavir performed better than lamivudine in each study, as highlighted--these are supposed to be pink I don't know exactly how it projects.

The next two lines display the two individual components that make up the overall histologic improvement score. Again, you can see that patients receiving entecavir achieved that endpoint significantly more often than those who received lamivudine. The last line of the study shows the secondary histologic endpoint of the Ishak fibrosis score. This is another method of evaluating liver histology. In this analysis entecavir was superior to lamivudine only in the lamivudine-refractory study, study 026. In the

treatment-naive studies the proportion of patients achieving an improvement in their Ishak fibrosis score was similar across the treatment arms.

This table displays some of the sensitivity analyses that were done by our statistical reviewers. The top line is a carryover from the previous slide and shows the primary analysis. In the primary analysis the only subjects who had evaluable baseline biopsies were included in the analysis. Subjects with missing or inadequate week 48 biopsies were counted as treatment failures. The sensitivity analyses, done by Dr. Hammerstron, included a series of different methods to impute the missing data for each of the Phase III studies. I am going to show you just two of the many analyses that he did.

In FDA sensitivity analysis C, missing or inadequate baseline or week 48 biopsies were excluded from the analysis. In this analysis, in study 022, the results were similar between entecavir and lamivudine and this is due primarily to the fact that more patients in the lamivudine

arm were excluded because they did not have week 48 biopsies. In the other two studies, again, entecavir achieved the primary endpoint significantly more often than patients who received lamivudine.

In sensitivity analysis D, this analysis includes all patients who were treated, not just those who had evaluable biopsies, but missing or inadequate week 48 biopsies were still counted as failures. Although the numbers are lower for all of these analyses, the difference between entecavir and lamivudine remains evident in each of the three pivotal trials.

This slide displays some of the analyses of secondary virologic, serologic and biochemical endpoints for the three pivotal trials. Again, the significant values are highlighted in the pink cells. In the Phase III studies a greater proportion of patients receiving entecavir than lamivudine achieved an HBV DNA PCR less than 400 copies/mL. Similarly, patients who received entecavir had a greater mean log decrease in PCR

from baseline to week 48 than did patients who received lamivudine. In the two studies that included e-antigen positive patients, studies 022 and 026, the proportions of patients who had a seroconversion were roughly the same. You will notice that in study 026 a relatively small number of patients actually met this criteria. Finally, in terms of the proportion of patients who reached a normalized ALT, again, entecavir was shown to be superior to lamivudine in each of the three pivotal trials.

We also conducted a number of subgroup analyses for baseline covariates of demographic or disease characteristics. The treatment effect of the primary endpoint was comparable for the covariates gender, race, age, geographic region, HBV subtype, baseline ALT, baseline bDNA or PCR, or by prior treatment with lamivudine or interferon.

Similarly, more limited subgroup analyses were performed to assess some of the key secondary endpoints. The treatment effect measured by the proportion of patients of subjects who achieved a

normalization of HBV DNA or those who achieved a viral load less than 400 copies/mL at weeks 24 and 48 were similar according to gender, race and age.

This slide displays a composite of the subgroup analysis for the Phase III studies. I really show you this for pattern recognition more than to display any kind of specific results. This slide plots the mean difference in treatment effect for the primary endpoint between entecavir and lamivudine, with 95 percent confidence intervals, for the three pivotal trials. This cluster represents study 026. This is 022 and this cluster is 027. In this display the horizontal line at zero percent represents no difference between the entecavir and the lamivudine arms for each of the baseline covariates that were evaluated. The cross-hatch mark is the mean, and as you can see, the vertical line is the 95 percent confidence interval.

In this analysis, every instance where the cross-hatch is above the zero line indicates an analysis that favored entecavir. Those with

cross-hatches below the zero line are an analysis that favors lamivudine. What I will show you though is that in all of these the confidence intervals are very wide and overlap, and this is what was seen in the subgroup analyses. There were no discernible differences but there were very wide confidence intervals between the different subgroups.

Now I would like to turn to our review of the safety conclusions. I would like to remind the committee that these were very large databases and there are minor differences in the analysis results between what you may have seen this morning in the applicant's presentation and in the numbers you may see in my presentation. These results and minor differences are due to slightly different methods of capturing different study windows and defining values that are used when there are multiple values within a study window.

In general, the FDA clinical review confirmed the safety and tolerability of entecavir as compared to lamivudine. No significant

differences in the rates or patterns of common adverse events or laboratory abnormalities were identified in entecavir-treated subjects compared to lamivudine-treated subjects. The rates of serious adverse events, discontinuations due to adverse events and deaths were very low across all of the studies.

Acute exacerbations of hepatitis as demonstrated by marked elevations of ALT, called ALT flares, are an important complication of HBV and its treatment. These were evaluated in more detail. Also, because central nervous system adverse events and malignancies were identified as possible toxicities from the animal studies, these events were also evaluated in detail. I will present some of the results of these analyses in the next few slides.

For this NDA, one interesting feature is that ALT levels were used as both a marker of efficacy and as a safety parameter. ALT flare was defined as an ALT value that was at least 2 times the patient's baseline value and also 10 times the

upper limit of normal. In discussing these ALT flares, one must remember that, particularly in the nucleoside-naive subjects, mean ALT values decreased from baseline to week 48 in both treatment groups. The mean decrease was about 100 international units from baseline to week 48 if the groups are taken as a whole.

In the nucleoside-naive subjects ALT flares occurring on study treatment were uncommon, 15/679, or about 2 percent, of entecavir subjects compared to 27/668 lamivudine subjects, or about 4 percent, experienced an ALT flare while on treatment. Though the numbers are very small, this analysis does favor the entecavir arm.

In studies 022 and 027 the study design allowed only subjects who met the protocol-defined response criteria to discontinue treatment and be then be followed off therapy. In these studies more subjects met that protocol-define response criteria in study 027 than in 022. Consequently, the analysis of off-treatment ALT flares represents a very selected subgroup of the patients enrolled.

That being said, compared to on-treatment ALT flares occurred slightly more often in both treatment groups, 15/414, or 4 percent, of

entecavir patients compared to 30/377, or about 8 percent, of lamivudine-treated patients. This analysis also favors the entecavir arm.

In lamivudine-refractory subjects, on-treatment flares were documented in 4/183, or 2 percent, of entecavir subjects compared to 19/190, or about 10 percent, of lamivudine subjects. Again, this favors the entecavir arm. In this study, 026, smaller proportions of the lamivudine-refractory subjects met the protocol-defined response criteria, discontinued therapy, and were followed of treatment. So, again, this represents a very selected subgroup in the study population. Off-treatment flares occurred in 3/56 entecavir subjects compared to 0/31 lamivudine subjects.

Central nervous system adverse events were identified in preclinical animal toxicity studies of entecavir. These events were closely monitored

in the Phase I and Phase II studies. In the Phase II dose-finding study 005, which was conducted in nucleoside-naive subjects, the incidence of grouped neurologic events increased with increasing doses of entecavir. Compared to a 7 percent rate of neurologic events reported in the lamivudine group, there were 11 percent of subjects in the 0.01 mg entecavir group; 19 percent in the 0.1 mg entecavir group and 0.5 percent in the 0.5 mg entecavir group reporting a neurologic event. There appeared to be trends but not statistically significant toward events of increased dizziness and insomnia in the 0.5 mg dose of entecavir.

However, in the Phase II lamivudine-refractory dose-finding study 014 a dose relationship with neurologic events was not identified, and in that study doses ranged up to 1 mg of entecavir.

We evaluated these events in all of the primary studies that were submitted, both individually and pooled as nucleoside-naive and lamivudine-refractory groups. This table displays

all neurologic events and individual events from the pooled study data. The rates of central nervous system events were roughly similar across the treatment groups of nucleoside-naive and lamivudine-refractory patients. These proportions represent patients who reported any central nervous system adverse event and selected events that are called psychiatric events. It is kind of an arbitrary cutoff in the currently used dictionary of adverse event terms.

However, if you look at the individual events, events such as anxiety, dizziness, headache, insomnia, migraines, paresthesia, somnolence and syncope were no different statistically across either the treatment groups or between the nucleoside-naive and lamivudine-refractory patients. If only subjects who were reporting grades 2-4 events, and those are moderate to severe events, were tabulated there was a slightly higher proportion of entecavir patients in the lamivudine-refractory study who reported grade 2-4 events compared to those patients

receiving lamivudine.

In looking at these patients individually, these differences can be accounted for by single patients who reported a variety of different moderate CNS events. It should also be noted that in all of these primary studies there was only a single subject who reported a grade 4 neurologic event.

Because entecavir was identified as a potential carcinogen in animal studies, the occurrence of malignancies has been tracked through all of the entecavir clinical trials. As of the last safety update during the NDA review cycle, 37 subjects had been diagnosed with a malignancy while participating in entecavir clinical trials. Most of these subjects were enrolled in the primary NDA studies, and these are 19/1,497 entecavir subjects, and 9/899 lamivudine subjects. In addition, there have been 9 subjects developing malignancies while enrolled in the special population studies. These studies include 038, the HIV/HBV co-infected subjects; 048, the subjects with decompensated

liver disease who contributed a disproportionate number of malignancies; and study 901, the large rollover continuing study. In these special populations there were 3 malignancies among patients receiving entecavir alone; 2 among subjects receiving adefovir alone; and 4 in the large group receiving a combination of entecavir plus lamivudine in the rollover study.

As might be expected, hepatocellular carcinoma was the most commonly reported malignancy. Malignancies that were reported in more than one subject in either treatment group in the NDA safety database included hepatocellular carcinoma in 7 entecavir subjects and 4 lamivudine subjects; basal cell carcinoma in 2 entecavir subjects and 1 lamivudine subject; breast cancer in 1 entecavir subject and 2 lamivudine subjects, 1 of whom had carcinoma in situ; and prostate cancer in 2 entecavir subjects. Of these patients who reported malignancies during the clinical trial, 6 of them were known to have had previous malignancies prior to entering the studies.

Now I would like to shift attention to our review of the virology resistance data. These data were reviewed by Dr. Lisa Nagra and Julian O'Rear

in our microbiology group. I will point out that the data that was reviewed in our NDA review included only data through 48 weeks so the numbers of patients that we have evaluated are somewhat smaller than the numbers that were presented in the applicant's presentation earlier this morning.

In our review, no genotypic or phenotypic evidence of entecavir resistance has been detected among 434 nucleoside-naive subjects analyzed at 48 weeks of entecavir treatment. These are patients in study 022 and 027. In that time period there were 2 subjects in study 022 who experienced a confirmed virologic rebound, but no genotypic or phenotypic evidence of entecavir resistance was identified in their HBV isolates. Follow-up data are needed after 48 weeks to determine the emergence of resistance of mutations in these patients and determine the pathway to entecavir resistance in treatment-naive subjects.

Lamivudine-refractory subjects are much less likely than treatment-naive subjects to achieve an HBV DNA less than 400 copies. Although this is true, reductions in viral load less than 2 logs and suppression below a viral load of 400 copies/mL can occur in subjects with

lamivudine-resistant HBV at baseline when they are treated with entecavir 1 mg. Lamivudine-resistance substitutions L8OV, L180M and M204V or I can emerge in the HBV of some patients receiving 1 mg of entecavir by week 48. These substitutions often arise in the context of mixtures at these sites and other lamivudine-resistance mutations at baseline.

Substitutions at amino acids I1169, T184, S202 and/or M250 are associated with entecavir resistance both individually and in combination. In all cases these entecavir-associated resistance substitutions emerged when lamivudine resistance mutations at L180 and/or M204 were present at baseline. And 14/189, or 7.4 percent, of evaluated lamivudine-refractory subjects treated with entecavir developed resistance mutations at 48

weeks. These entecavir-associated resistance substitutions were associated with virologic rebound in 3/14 subjects by 48 weeks and additional subjects experienced rebound with prolonged therapy beyond that time.

Lamivudine-resistant HBV clinical isolates at baseline and from studies 015, the transplant study, and 026 showed a 3-51-fold reduced susceptibility to entecavir by in vitro assays. HBV developing entecavir-associated resistance substitutions in the clinical trials were susceptibility to adefovir in vitro but remained resistant to lamivudine. Finally, adefovir-resistant hepatitis B was susceptible to entecavir by in vitro assays.

Our virologists' conclusions were that no entecavir resistance has been detected in nucleoside-naive subjects treated with entecavir through 48 weeks, but longer-term follow-up data are needed.

Entecavir resistant mutations can emerge on entecavir treatment when lamivudine mutations

are present. These emerge at a rate of less than 10 percent at 48 weeks. These entecavir resistance mutations are associated with virologic rebound and, finally, entecavir is cross-resistant with lamivudine but not adefovir by in vitro assays.

Now I would like to turn attention to the risk-benefit assessment of entecavir and the proposed pharmacovigilance plan. I would like the committee members to consider these issues very carefully and provide feedback to us during the discussions this afternoon.

In the evaluation of risk-benefit we must balance the potential benefit of an effective drug for a serious disease against an unknown risk of cancer. It has been well documented that patients with chronic hepatitis B have increased risk of hepatocellular carcinoma and new cohort studies suggest that they may have an increased risk of other malignancies as well.

There is accumulating evidence that treatment of chronic hepatitis B may decrease the rate of progression of liver disease and may delay

or prevent hepatocellular carcinoma. Entecavir has demonstrated efficacy in the treatment of chronic hepatitis B as measured by liver histology, HBV DNA and other endpoints. Its efficacy was better than or equivalent to lamivudine in all of these analyses through 48 weeks of treatment. The general safety and tolerability profile of entecavir was similar to that of lamivudine.

Positive carcinogenicity findings in animal studies are not rare and they are usually described in the product label, usually in a special section for carcinogenicity, mutagenicity and impaired fertility. Animal carcinogenicity studies identify a hazard signal, as Dr. Farrelly pointed out earlier, and cannot be directly extrapolated to a level of risk in humans. Quantifying this level of human risk is very difficult. The mechanism of carcinogenicity is likely to be different for each different drug. Consequently, the FDA has traditionally considered these risk-benefit assessments on a case-by-case basis. Higher perceived risk is tolerated among

drugs for diseases with serious and life-threatening consequences.

BMS has proposed a comprehensive pharmacovigilance plan for entecavir. This plan includes increased monitoring and analysis of post-marketing safety reports and regular reporting of the results of these analyses to the FDA. It also includes continued tracking of subjects in clinical trials through the ongoing rollover and observational studies. Finally, BMS has proposed a large simple safety study to evaluate the occurrence of major events as entecavir moves into broader clinical use.

We have reviewed a draft protocol for this post-marketing safety study and discussed the proposal with our colleagues in the Division of Drug Risk Evaluation, Office of Drug Safety. We agree that the proposed study has a number of strengths and represents a good effort on the applicant's part to collect important safety data.

The strengths of the study include the fact that the study design is randomized. It

includes an active control group; stratification by prior treatment; pertinent endpoints and pre-planned analyses. The study will evaluate an international population who are using the drug in a real-life setting. it will allow enrollment of patients with concomitant hepatitis C and HIV, and enroll a patient population with a broader spectrum of hepatitis B disease than was seen in the clinical trials. The size of the study, 12,500 patients, and enrollment through many local physicians, each following a relatively small number of their own patients will be advantageous.

However, we also recognize the potential limitations of the proposed study. The length of the study may not be adequate to identify malignancies with a long latent period. There may need to be some mechanism of ascertaining events over a longer period than is currently proposed. Results may be confounded as subjects may switch from the originally assigned treatment to the comparator group over time. Certainly, the number of patients lost to follow-up may be higher than

anticipated. In this case, no specific tumor type can be targeted for surveillance and, clearly, there is no way to stratify for all the other possible co-factors for malignancies that might be encountered in the study population.

That being said, the study would be similar in size and scope to some others that have been requested by the FDA or that have been used to identify other risk factors. The study might identify changes in 5-8-year risk of hepatocellular carcinoma or other tumors in patients receiving treatment for hepatitis B. Importantly, however, negative findings at the end of the study may not equate to a conclusion that there is no risk.

I would like to put the entecavir animal carcinogenicity findings in context of other drugs that have been reviewed in our division. As Jim pointed out, we see nucleoside analog drugs on a fairly regular basis. We have made risk-benefit assessments for drug approvals and for the need for follow-up on a case-by-case basis based on the robustness of the animal data and the disease being

treated.

Zidovudine, the first approved anti-retroviral drug, was shown to result in vaginal tumors in rodents. The division considered the devastating consequences of untreated HIV to far outweigh the potential risk of cancer in this population. However, in the setting of zidovudine being used for the treatment or for the prevention of perinatal transmission of HIV, many of the infants exposed to zidovudine will not be infected. In this case, infants exposed to zidovudine perinatally are being followed in a long-term prospective outcome study conducted by the NIH. This is in PACTG study 076 and 219.

Many of the nucleoside reverse transcriptase inhibitors and a number of the protease inhibitors, such as ritonavir, have shown positive findings in animal carcinogenicity studies. A similar rationale led to the acceptance of this risk in humans using these drugs.

Ganciclovir and cidofovir, both approved for the treatment of serious CMV infections, are

also among the drugs with positive animal carcinogenicity findings. The division again considered the consequences of untreated CMV to outweigh the potential for human cancer. However, both of these drugs contain in their labels a boxed warning that includes the animal carcinogenicity findings.

In the case of famciclovir, a drug used for the treatment of less serious herpes simplex infections, the animal findings were considered a very weak signal and not relevant for human clinical use.

The Division of Antiviral Drugs is not the only review division to debate the clinical relevance of positive animal carcinogenicity findings. Drugs with positive findings have been approved for a variety of other indications, including but not limited to lipid-lowering drugs, anticonvulsants, and drugs for osteoporosis, ADHD and gastroesophageal reflux. For some of these drugs long-term clinical trials have shown no imbalance in cancer rates. Some of the drugs were

approved many years ago, before animal carcinogenicity studies were available, and have subsequently had significant long-term use experience. In some cases completed epidemiologic linking studies have given conflicting results.

In some cases, however, the FDA has requested post-marketing studies to further assess the risk of human cancer in approved drugs. Some of the types of requested post-marketing evaluations include a long-term prospective observational study of a drug compared with an appropriate control; registries of patients using a drug long term; post-marketing surveillance program; and a retrospective cohort study to measure the incidence of a specific tumor in the contribution of drug.

In conclusion, we will like to say that we believe that in well-conducted clinical trials entecavir was shown to provide efficacy compared to lamivudine for the treatment of chronic hepatitis B as measured by multiple histologic, virologic, biochemical and composite endpoints. The treatment

benefit of entecavir over lamivudine was greatest in lamivudine-refractory subjects. The general safety and tolerability of entecavir was similar to lamivudine in all populations studied. Similarly, the safety and tolerability profile of entecavir was similar in nucleoside-naive subjects who received 0.5 mg dose and lamivudine-refractory subjects who received 1. mg dose.

Nonclinical studies have identified entecavir as carcinogenic in mice and rats. However, the clinical relevance of these animal carcinogenicity studies are unknown. To date, no increase in human malignancies has been identified in the clinical trials. BMS has proposed a large simple safety study designed to identify increased cancer risk in patients receiving entecavir as part of a comprehensive pharmacovigilance program.

We believe that entecavir fits in a unique position. Based on the animal carcinogenicity studies, it may pose some increased risk of cancer. However, its treatment effect in chronic hepatitis B may actually lead to a reduction in

disease-related hepatocellular carcinoma. The review team believes that the proposed post-marketing study and pharmacovigilance plan may provide a good opportunity to evaluate the long-term effects of entecavir, and we are looking forward to hearing the discussion from members of our committee and consultants this afternoon.

I would like to finish with just a quick run through of the questions we will pose to the committee this afternoon so that you can keep these in mind if you have other questions you would like to pose to either me or Bristol-Myers Squibb.

Question 1, how would you assess the risk-benefit of entecavir in the context of the available clinical safety, efficacy, resistance and nonclinical carcinogenicity data?

Question 2, does the risk-benefit assessment for entecavir support the approval of entecavir for the treatment of chronic hepatitis B in adult patients? If the answer to 2A is no, what additional information would be needed to support a resubmission?

If the answer to 2A is yes, discuss whether the results of the rodent carcinogenicity studies should impact the indication and usage

section of the product labeling.

B, based on the available data, discuss the potential role of entecavir in the HBV treatment armamentarium.

Question 4, assess the potential risks and benefits of proceeding with development of entecavir for the treatment of chronic hepatitis B in pediatric patients.

B, what, if any, additional information is needed in order to proceed in this age group?

Question 5, discuss the applicant's proposed pharmacovigilance plan to address human cancer risk, including comments on the design of the proposed large simple study.

Finally, question 6, are there other issues that you would like to see addressed through post-marketing commitments?

Thank you, and I will take questions along with Dr. Farrelly.

Discussion

DR. ENGLUND: Thank you, Dr. Lewis and the FDA committee for giving us a nice summary, succinct and pretty clear.

At this point, from the committee, we are going to entertain questions directed only to the

presentations you have heard this morning. We are not going to discuss the questions that were laid out for us. That is for this afternoon and we are going to have a whole afternoon in which to do that so this is a relatively limited and focused discussion and I am happy to ask for questions from the floor. Dr. Paxton?

DR. PAXTON: I have a very brief question. Could you just explain for me what is the FDA's criteria for having a boxed warning versus a mention?

DR. LEWIS: I am actually going to defer that question to Dr. Birnkrant, our division director.

DR. BIRNKRANT: When we helped to construct the labels for cidofovir and ganciclovir

we took into account, with regard to a box warning, the effects of the drug in the animals such that in those two drugs in particular the tumors appeared at multiples of human dosage either less than 1 or very close to 1. So, we thought that was highly significant. Whereas, in this drug the tumors appear at much higher multiples of human dose. So, based on those findings, in the ganciclovir and cidofovir carcinogenicity studies were placed in a boxed warning.

DR. ENGLUND: Dr. Haubrich?

DR. HAUBRICH: This may be a question for the applicant, but in the pharmacovigilance program how will you address the issue if patients either drop out or refuse to be randomized, given the efficacy data which clearly shows this drug is better than certainly lamivudine?

DR. MORGAN MURRAY: Dr. Pierce will address the questions on enrollment and dropout and how we intend not to lose patients to follow-up.

DR. PIERCE: Thank you. There are several mechanisms of handling dropouts or of switching

really in this. The way we have thought through this--and certainly as mentioned this is a draft proposal and we are willing to take other suggestions to modify this plan--our plan, in the worst-case scenario, if people are dropping out at high rates, is that we will then be left with an observational study which, in and of itself, will have great power to give us a rate which we can then compare to a background rate of malignancies.

We concur with you that there may be difficulties in randomization. We do, however, plan in this study to have randomization against the standard of care so whatever alternative therapies are available within that country, patients will have access; it is not randomized to lamivudine only for example.

DR. HAUBRICH: Just a quick follow-up, is drug going to be provided for either arm?

DR. PIERCE: Those levels of details have not been really worked out.

DR. ENGLUND: Dr. Wood?

DR. WOOD: In the sponsor's proposed

post-marketing study, the FDA comments that the study might identify changes in a 5- to 8-year risk of hepatocellular carcinoma and other tumors. I was wondering, from the FDA, from the experts that are present or from the sponsor, do we have any current estimates of the 5- to 8-year risk of hepatocellular carcinoma and tumors in patients with HBV who are untreated and then those who are treated, so that we might have an assessment of what that risk is.

DR. LEWIS: BMS actually does have data that they can present according to that.

DR. MORGAN MURRAY: Dr. Pierce?

DR. PIERCE: I think to respond to that we will go back to that slide I showed this morning, the 15-20 slide. This slide used projections of the rates of HCC based on the experience in the Taiwan data set. These are similar patients to those that meet treatment guidelines. These are individuals who have a viral load of greater than 10 5, greater than or equal to 105. So, that is why you may see this particular estimate of the number

of HCCs that you would see over a five-year period that may be higher than what you see in other cohorts because this is dependent on the treatment guidelines essentially.

DR. WOOD: Do we have any data in treated patients at all? The duration of treatment with lamivudine has been somewhat more limited and maybe not as extensive but it would be interesting to see whether or not--I don't know if any data exists regarding treated patients and whether or not that is significantly lower because that might impact the ability to detect this excess incidence of cancers since everyone would be treated in the post-observational study?

DR. MORGAN MURRAY: Dr. Wilber, please?

DR. WILBER: Richard Wilber. The study referenced this morning in the original background presentation, and I am sure a number of you are familiar was the Liaw study which compares, according to the question, treatment versus placebo. It does not give you the range of time that you asked about since the study was terminated

at 32 months. Within that study there was adequate time to assess the difference in HCC in lamivudine-treated patients versus placebo. Although a number of the HCCs appeared to have occurred early, and when those are dealt with not simply as events on study but when they are assessed whether they might have actually been antecedent to study beginning, the significance drops off between the two. There were many other endpoints in disease progression and the treatment benefited those far more noticeably, if you will, than the event of HCC. Dr. Dienstag, do you have anything else to add? You are probably a little closer to those data.

DR. DIENSTAG: Jules Dienstag, Massachusetts General Hospital. One of the things to keep in mind about the study is that it was a prospective study designed to monitor differences between the treated and untreated groups. The study had to be terminated at 72 weeks because the difference was so substantially different. Had they been able to continue the study, then the

marginal difference--I mean, hepatocellular carcinoma almost certainly would have been more statistically significant, but that is the limitation of having a data safety monitoring board to protect patients.

DR. MORGAN MURRAY: Dr. Di Bisceglie, anything else to add about hepatocellular carcinoma?

DR. DI BISCEGLIE: Adrian Di Bisceglie, St. Louis University. I think that I would fully expect a reduction in hepatocellular carcinoma over time. I think your question is how long would it take before we begin to see that. I think it will take at least two or three years. We may begin to see a difference at that time, but the difference will become more and more evident with time with an agent that suppresses virus to a great degree and is not associated with resistance. One of the points in the Liaw study was that with lamivudine as resistance began to appear, so the clinical benefit began to be lost.

DR. ENGLUND: Thank you. Dr. Bartlett?

DR. BARTLETT: Do you have any plans to study this drug in pediatric populations or during pregnancy?

DR. LEWIS: We will get into this a little bit later as we discuss the questions, but based on the preliminary animal carcinogenicity data and uncompleted Phase III adult trials, the FDA asked BMS to delay starting studies in pediatrics until we had a fuller understanding of the risk-benefit before starting.

DR. ENGLUND: Dr. Paxton?

DR. PAXTON: Yes, I had a question about decompensated patients. It looks to me like in the previous studies most of the patients were compensated. What are your plans? Will decompensated patients be included in the pharmacovigilance studies that are going on? Do you have plans to look at them in any other form as well?

DR. MORGAN MURRAY: Yes, we will include a broader patient population and, as Dr. Lewis alluded to, we do have an ongoing study in patients

with decompensated liver disease with comparison of entecavir and adefovir. We have, as Dr. Lewis mentioned, conducted an interim analysis on 50 or so of those patients that have completed 24 weeks of treatment. The study is intended to enroll 270 patients and we would be happy to share those interim data, again recognizing that it is a very small number of patients.

DR. PAXTON: And as a follow-up, do you expect to see a markedly different malignancy rate between the compensated and the decompensated patients in the trial?

DR. MORGAN MURRAY: As Dr. Lewis alluded to, these patients in general will have a higher malignancy rate.

DR. ENGLUND: Dr. Bell?

DR. BELL: I have one other question for Bristol-Myers Squibb on some of these cancer data. You previously showed on your slide 62--you referred to a U.S. cohort and a Taiwan cohort in which you were estimating the incidence of HCC and other tumors. I wonder if you could, please, give

us a little more information about the source of those data and who the people are in these cohorts.

DR. MORGAN MURRAY: Yes. Dr. Brett-Smith, can you provide some more information, please?

DR. BRETT-SMITH: Let me take the U.S. cohort first. The U.S. cohort is actually based on a historical database derived from Kaiser in northern California, so primarily the Oakland system there, and the Henry Ford Hospital system in Detroit. This was, again, sponsored with a grant to the independent people who manage those databases, and they conducted a review of their historical patient data from 1995 to 2001. They identified a cohort of confirmed surface antigen positive patients within that database. Then they cross-referenced it with their entire medical record database, and also with the cancer registries and with death certificates. From that data set they developed a rate of cancer incidence over the entire cohort. This is a cohort that we do not have good information about the proportion treated, non-treated, the mix.

The Taiwan cohort is structurally quite different. This was a community-based prospective observational study sponsored by the Taiwan

Ministry of Health. It was actually looking at overall cancer incidence. Because of the demographics of the population locally, obviously, hepatitis B infection and HCC were important issues. They enrolled subjects over 1991 to 1992, and they actually evaluated them and have continued to follow them to the current time. Our data cut was taken in June of 2004. Again, they performed all analyses and maintained the database.

In that data set there are a couple of important factors to note. The first opportunity or the first availability for hepatitis B nucleoside treatment was in 2003. So, this is essentially more of an untreated cohort. There was more specific and directed screening for HCC within the general surface antigen positive population, and specifically for patients who were identified as having cirrhosis. So, there are caveats around these comparisons. They are the best ballpark

estimates for comparison that we were able to have.

DR. ENGLUND: Before you step down, I have just one quick related question. Did that study cohort then include children, or was it just adults for both of those studies?

DR. BRETT-SMITH: Both are adults only.

DR. ENGLUND: Mr. Grodeck, you had a question?

MR. GRODECK: This question is for Dr. Lewis. So that we can get some context in terms of the cancer, potential cancer risk, you showed us a slide on adefovir. I noticed that there were some limitations in dosing adefovir. To give us some perspective how it might compare to similar dosing for entecavir, can you talk a little bit about those limitations?

DR. LEWIS: Well, I think Dr. Farrelly pointed out the major limitations. These studies are generally conducted at the MTD, maximum tolerated dose that the animals will tolerate over a period of the two-year study. In many cases a pilot study is done to identify that MTD but with

adefovir, because of its known renal toxicity, the study could only achieve a certain level of dosing in the rodents which was modest compared to the levels that could be achieved in either the lamivudine carcinogenicity studies or the entecavir carcinogenicity studies. It is very different, even with using relatively standardized animal models, to directly compare across studies because the general toxicity of the different compounds is quite different and the target organs may be different.

MR. GRODECK: So can a similar cancer risk be eliminated for adefovir in the same arena?

DR. LEWIS: I would imagine that you would have to look at people who are on hemodialysis to try and figure that out. I really don't know. I don't think you can say it is eliminated; it just can't be studied.

DR. ENGLUND: Dr. Wood had a question.

DR. WOOD: My apologies, it is going back to the post-observational study and this is really a question for the statisticians. Since we don't

know the exact diminishment of what the risk for hepatocellular carcinoma may be in treated patients, is there a lower threshold number below which the 12,500 projected participants would be insufficient to detect an excess cancer risk? So, if it is 8 is 12,500 still going to be adequate to detect that excess cancer risk potentially, or is it going to have to expand to 15,000? That is what I am looking for, some lower threshold.

DR. MORGAN MURRAY: Dr. Pierce can speak to what our power to detect will be with that patient population.

DR. PIERCE: I want to make sure this powering that I mentioned is principally for the non-HCC malignancy because really I think that is the question on the table. So, that is really the primary goal of this study. However, what I had wanted to point out, and I think your previous question hinted in that direction, is that those rates that I showed for the HCC were in the non-treated group so that may shrink since both groups will be on treatment to show a diminution in

those rates between arms. But the primary objective of this study is those non-HCC cancers.

DR. ENGLUND: Thank you. Dr. Seeff?

DR. SEEFF: I wonder if I can get back to the question I posed this morning to see whether, in fact, we have the information about the relationship between the primary and the secondary endpoints, and specifically the composite outcome, and maybe FDA has done that as well. I did see the composite review but it did not include I think the histology. So, what I am asking is what happens histologically, virologically and biochemically when you treat with entecavir, and how does it compare to lamivudine?

DR. MORGAN MURRAY: We are doing those analyses. I am just going to double check, are we ready to discuss them or do we need some time over lunch? I mean, literally, they are plugging away as we are sitting here. Dr. Lewis said she will start and then Dr. Brett-Smith is prepared to show you what we have.

DR. LEWIS: In the FDA analysis we did not

include histology in our composite endpoints. We compared virologic and biochemical analyses, serologic and biochemical analyses. We did not include histology in that. However, we are in the midst of actually a larger project using both the adefovir database and this entecavir database to look at many different combinations of outcomes and predictors of outcomes but at this point we have not completed that because of the time frame required for this review.

DR. SEEFF: Let me just be sure that my question does not impugn this drug. There is no question that it is a very effective drug in reducing the viral load. But it seems to me that ultimately the FDA, I think, is going to have to re-think the way it analyzes outcome. I feel sure that in the future we are going to have to have a composite score to be able to be sure that we understand. If we don't look at histology and yet histology is the primary endpoint, I don't quite understand why we don't, in fact, include that in the composite score. It just doesn't make sense to

me. Obviously, this is not the place to discuss this. We are going to have other meetings to come up with perhaps better ways of assessing outcome, but histology is just not in it at the moment.

DR. LEWIS: I think we will probably be discussing this in great detail at a future meeting to discuss consensus hepatitis B treatment and study design.

DR. ENGLUND: One last question?

DR. MORGAN MURRAY: Dr. Brett-Smith is prepared to show that composite analysis.

DR. BRETT-SMITH: We actually did two analyses for you looking at both virologic endpoints. We used the PCR data in both. So, if we could show slide 17-1? The 022 naive e-antigen positive study is on the left, naive e-negative is in the middle, and refractory is on the right. The top line presents those who have histologic improvement and ALT normalization and a DNA less than 400, so the most rigorous virologic endpoint. The lower line is related more to the current management guidelines and our own management

guidelines within the study, and does the same analysis, this time with the PCR database, not the bDNA database but using a cutoff of less than 10 5 copies/mL.

Again, the relationship and the pattern of results for entecavir versus lamivudine is consistent. Overall, the total response rates are obviously lower by this criterion, and I think it reflects some of what you see in the background document around this sort of issue of correlation across those week 48 endpoints.

DR. MORGAN MURRAY: Dr. Cross, do you have something to add?

DR. CROSS: Just in case the second question is are the differences significant, yes, they all support superiority for entecavir.

DR. ENGLUND: Could you state your full name?

DR. CROSS: Anne Cross, Bristol-Myers Squibb.

DR. ENGLUND: Thank you. One last question from Dr. Fish.

DR. FISH: For the applicant, returning to the pregnancy question, if I may, you reported I think a low number of 41 pregnancies and 1

unfavorable outcome. The first question, is there animal pregnancy data? Second, I was surprised by the termination rates and I am just wondering if this is similar to rates seen in other hepatitis B studies, or perhaps related to culture differences and regional differences where the terminations were occurring, or whether these were perhaps encouraged by the investigator out of fears of the drug.

DR. MORGAN MURRAY: First I will ask Dr. Lois Lehman-McKeeman to address data in animals.

DR. LEHMAN-MCKEEMAN: Nonclinically, as part of the development of entecavir, it was evaluated for embryo toxicity and teratology endpoints in both rats and rabbits. Essentially, what those data indicated is that in rats there was evidence of some embryo toxicity only at dosages that were maternally toxic. When we interpret these studies that is an important finding relative

to the presence of maternal toxicity. Those dosages that were associated with that effect were at least 180 times the human exposure. In rabbits there was again little evidence of embryo fetal toxicity. It was at an exposure of about 800 times human exposure when it first presented. So, the nonclinical data suggests no signal for teratologic or adverse developmental outcome.

DR. MORGAN MURRAY: And Dr. Brett-Smith will address your question on the clinical outcomes and how they compare with other studies.

DR. BRETT-SMITH: In our database and in our pregnancy CRF forms we do not collect actual data as to the reason for a termination. Therefore, what I am saying is somewhat speculative is but based on our global experience in the virology group of conducting multinational trials. And it is important to recognize that, again, there are many different factors involving, you know, areas outside the U.S. and what is contributing to these termination rates. In a global sense, as an individual looking at these results across some of

our other virology programs including HIV, these early termination rates did not strike us as concerning. I am sure that there are multiple individual factors for the woman who is pregnant, including some concern about uncertainty.

DR. ENGLUND: Well, thank you, everyone. There will be some more time for questions after lunch. Before we leave, I would like to remind the committee to refrain from discussing any agenda items or meeting-related questions with each other or with the sponsor during the lunch hour. There is, in fact, a table reserved in the restaurant in the lobby of the hotel for the committee members where you can have a seat and pay for yourself. Thank you. The meeting is adjourned for lunch.

[Whereupon, at 11:57 am., the proceedings were adjourned for lunch, to reconvene at 1:05 p.m.]

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A F T E R N O O N P R O C E E D I N G S

DR. ENGLUND: Welcome back to the continuation of the new drug application 21-797 and 21-798 for entecavir tablets and oral solution. At this point we have an opportunity for an open public hearing, and no one has previously registered to have themselves heard, and I would just like to make sure that there is no person present that would like to have a discussion as part of this open public hearing. If not, then we won't have it and we will go on to the next discussion and at this point I would like to ask Dr. Debra Birnkrant to come up and give us our charge.

DR. BIRNKRANT: Good afternoon and welcome back to the advisory committee meeting. What did we hear this morning? We heard that chronic hepatitis B infection is a serious disease, with very limited treatment options. You also heard I believe that the agency and the applicant agree on the safety and efficacy findings. We also heard about issues related to animal carcinogenicity

findings.

Now, this is a very unique situation because we have a disease caused by hepatitis B virus which, in and of itself, has been characterized as a carcinogen, and we have a treatment that appears to be highly effective and safe but happens to have positive animal findings. There is also literature that was mentioned, and those references support that treatment with decreasing hepatitis B virus DNA may actually translate into perhaps a decreasing cancer risk.

So, what is the bottom line? The bottom line is that the relevance to humans with regard to the animal findings is unknown and at this point in time we can't really quantitate the risk. But what can be done is further study and then we will specifically be asking you about the applicant's proposed pharmacovigilance study which is a part of their pharmacovigilance program.

So, with that, I would like to turn it back to Dr. Englund for the discussion period prior to the question and answer period. Thank you.

DR. ENGLUND: Thank you. I just want to make sure, before we go to the specific questions for the committee--we have one or two minutes if

there are short questions that anyone has that we didn't address before lunch. Dr. Sun?

DR. SUN: Yes, I have a question for Dr. Farrelly which he may or may not be able to answer, but to the extent that he can describe the rationale of the CAC committee opinion, why did 16 or 17 members--what was the rationale for the opinion on the mouse lung tumor findings? Why was the vote so positive in terms of the clinical relevance? My question is did they not find the mechanistic explanation that the sponsor proposed to be compelling?

DR. FARRELLY: Yes, most of us did I think. Most of us felt the explanation was quite compelling. Some said it wasn't proven but in general it was pretty good. There was some concern about people who smoke taking entecavir who don't have the same lungs as people who don't smoke. They will have some cells that are turning over in

the lung. They may have some macrophage invasion. I think the point was that most of the people on the committee felt that, yes, there was some human concern about a drug that does induce tumors in an animal models whose cells are proliferating. I think if you look at some of the drugs that induce cytochrome p450, many of those drugs are liver carcinogens and one of the reasons may be because what they are doing is they are making the liver turn out these enzymes and for the lifetime of an animal whose liver cells are turning over, and over, and over, one sees tumorigenesis. So, I think most people felt that for the people who might be smokers there might be some risk, but in general I would think there is very little risk for folks who aren't smokers. Now, in Asia there is a very high percentage of people who smoke. I think that was much of the reasoning, although I can't get inside the head of everybody.

DR. ENGLUND: And one other question by Dr. Bell?

DR. BELL: Yes, just another brief

question, you mentioned earlier the difference in the magnitude of how carcinogenic some of the other antivirals were compared with this drug--

DR. FARRELLY: Right.

DR. BELL: --and to the extent that you can help us even further put that into context, at least that would be helpful to me, you know, how "bad" is this in comparison to other similar compounds?

DR. FARRELLY: Most of the tumors that arise here arise at fairly high multiples of the human exposure. We usually go by three different ways: The comparison of nominal dose between the animals and humans, which is usually the worst way; body surface area, body surface area is pretty good for drugs that are not metabolized and that are eliminated by body surface area phenomena. So, for drugs that are not metabolized and are passed through the kidney body surface area is usually a very good way to do it. But the exposures in the animals and the exposures in the clinic are known for this drug so we use the exposures. For a lot

of the other drugs we have done the exposures.

To give an example of two of the drugs that we have boxed warnings for, one of them is cidofovir and this is the drug that is approved for hepatitis--no, it is adefovir; it is a relative of adefovir. It is a nucleotide analog that is fairly similar in structure. When the drug was being developed for CMV retinitis in AIDS patients the studies were stopped for a while because it was found in a three-month study in rats that after six doses, one dose a week for six doses, palpable mammary adenocarcinomas could be found in the animals. The argument was made that they are probably there because the drug actually was given to the animals subcutaneously and it was felt that mammary tissue was being flooded by higher concentrations of the drug. So, we asked that a different route of administration be used so the sponsor did intravenous administration and, lo and behold, the same tumors showed up again.

When we looked at the exposure in the animal studies compared to the exposure in the

clinic, it was much lower than 1. I mean, it was very difficult to calculate; it was about 0.1. So, we felt that there was great concern over that drug because it gave tumors that killed all the rats in really short-term studies. So, there are no carcinogenicity studies carried out on cidofovir. Although we do have in the label that in a one-year study in monkeys there were no tumors seen, but there were only a few monkeys in that study so it is hard to say. That is not a carcinogenicity study and that is pointed out.

Ganciclovir is very similar. It is a CMV retinitis drug. It is interesting that ganciclovir and cidofovir are for the same indication. Ganciclovir gave a very high incidence of tumors in lots and lots of tissues in the mouse at a tenth of the exposure in the clinic or at 1.-something the exposure, about 1-fold the exposure. There were a lot of tumors, a lot of mouse specific tumors in tissues that don't exist in the human. Rats don't have a gallbladder so you will never see a gallbladder tumor in rats--you know something is

wrong if somebody examined the gallbladder. But we were very concerned that a lot of different tumors showed up and many of the tumors were vaginal tumors but at very, very low doses, and those are the things we look for when we are trying to get a comparison between the animal studies with the clinical studies.

As was mentioned earlier, we do the same thing for the reproductive toxicity studies so that when entecavir was looked at in reproductive toxicity studies you only saw really bad results when there was lots of toxicity to the dams. What we usually look for is at doses lower, where there is no toxicity to the dams even though it is maybe 50-fold or 10-fold or, probably in this case, 100-fold and if we see nothing that indicates the type of things that we saw with the toxicity in the dams we are much less concerned.

So, as Debby or Linda said, on a case-by-case basis you look at the studies. This drug gives tumors. The studies were good. The studies were carried out very nicely. It gave

tumors, but most of the tumors were at fairly high doses and, like I said and like Dr. Sun said, it looks like the company made a pretty good case for lung specificity in mice although it is not proven. Does that help?

DR. ENGLUND: Thank you. Dr. Munk?

DR. MUNK: Yes, I have a question about the distribution over time of the malignancy diagnosis. There is a figure in our binder on page 84, figure 7.5.2--

DR. ENGLUND: This is the sponsor background.

DR. MUNK: --saying that the greatest number of new diagnoses was made between weeks 24 and 48 showing a similarity between entecavir and lamivudine and that they levelled off and go essentially almost down to zero after 72 weeks. I guess I would just like some explanation of that. It says "may reflect the on-study diagnosis of tumors that were latent at the time of enrollment." Now, does this imply that it took a while for the drugs to have an anti-tumor effect, or does it

imply somehow that the treatment stimulated the tumors into a state of activity where they could be diagnosed?

DR. MORGAN MURRAY: I would like Dr. Di Bisceglie to comment on that, please.

DR. DI BISCEGLIE: Adrian Di Bisceglie. What I can comment on are the hepatocellular carcinomas, not the other cancers. To look at this, I had done an analysis of the tumors that developed in the study cohort. There were 11 patients with HCC. Of those 11, there were 6 in whom the tumor size was known at the time of diagnosis.

Is that slide available, my slide? Thanks, if you could put that up for me. What I did with those tumor sizes is, based on these known data of growth rates of HCC--this is from published data in Taiwan based on increased tumor diameter by ultrasound--you see that the median doubling time of HCC is 117 days. The range is from 29 days up to about 400 days. So, first, there is a broad range. But what I did was I took the worst-case

scenario, what if this was the most rapidly doubling tumor, 29 days, and I looked at these 6 tumors and tried to figure out when they may have arisen.

Each of those lines represents 1 of the 6 cases. They are numbered, 1, 2, 3, 4, 5, 6 whether they were receiving lamivudine or entecavir, and the top diamond shows the tumor volume, not the tumor diameter but the tumor volume. If we take tumor doubling time of 29 days, that worst-case scenario, and then backtrack to when the tumor arose when it was about 1 mm in diameter, you will see that in 5/6 cases we would predict it would have arisen many months prior to the onset of therapy.

Next slide. Finally, this one tumor that was the latest developing, if you take the median doubling time, not the worst-case scenario but the median doubling time, you can see that tumor might be predicted to have arisen nearly two years prior to the onset of therapy. So, that is what I can address.

DR. MUNK: I guess my question is why are they not detected when patients enter the studies, and is this perhaps an issue of them being

monitored more closely after they are in the study, or what is going on her?

DR. MORGAN MURRAY: Dr. Brett-Smith?

DR. BRETT-SMITH: The entecavir studies actually did minimal monitoring for tumors prior to study entry in the sense that we wanted to see all-comers. Therefore, we did have alpha fetoprotein criteria but, beyond that, and if people were over an alpha fetoprotein of 100 you had to have an ultrasound to screen. Other than that, there was not routine ultrasound screening done so many of these patients came in with no screening particularly for HCC.

The point of the comment about some of the tumors, whether HCC for which I think you have heard a nice argument, or non-HCC might precede the onset of enrollment to the study is, I think, an issue in any cohort that sort of comes into medical care and then is followed.

DR. ENGLUND: Thank you. This is absolutely the last question but I know you didn't get a chance before.

DR. GERBER: It is a very short question, just related to the post-marketing surveillance for ganciclovir. Is there any signal that caused

increased tumors in people or not?

DR. LEWIS: There was no specific post-marketing study required after the approval of ganciclovir. At the time, there was no other treatment approved for CMV retinitis in HIV patients and those patients' survival was very limited after that period. So, there has been no formal study but there has clearly been more extensive use of the drug and, as far as we know, there has not been any report of an epidemiologic study linking increased tumors.

Questions to the Committee

DR. ENGLUND: Well, thank you, everyone. We are now going to proceed to our questions. For at least the first two questions I will read the question and I would like to have us go around the

table just to make sure everyone has time to say or ask a question or give an opinion. This is not a vote. This first phase is the discussion phase for question number 1.

Question No. 1

Question number 1 is how would you assess the risk-benefit of entecavir in the context of the available clinical safety, efficacy, resistance, and nonclinical carcinogenicity data?

For this period you really only get two minutes so it is not that you get to expound a whole lot but we would like to hear your opinions, your concerns. We have some experts in different fields on the committee and it would be really helpful to have people address some of the things that their expertise addresses. So, with that, I think I am going to take the chairman's prerogative and, Dr. Schwarz, you are going to be nominated to go first, if you don't mind.

DR. SCHWARZ: Well, I have prepared a series of comments for the specific role of possible future pediatric studies so I think I will

defer to that.

DR. ENGLUND: Great, and we need those but why don't we go on? Dr. Bell?

DR. BELL: I am also not sure that I am the right first person to comment on the answer to this question in that a lot of my expertise is more in the epidemiologic aspects of this rather than the clinical aspects.

DR. ENGLUND: You can come back later. Dr. So?

DR. SO: I guess I have to say something, right? I think the sponsor has demonstrated that this is a very effective drug in suppressing HBV replication. Based on the data presented, I think, apart from the potential carcinogenicity problem, it seems like a pretty safe drug for treatment of this problem.

I agree with some of my colleagues that, you know, with these drugs over time, even though at the moment you don't see any development of resistance or mutants at one year, with time I am sure you are probably going to find more of that.

If you look at the group where entecavir was used in the treatment of lamivudine-refractory patients, you can already see that at one year. The FDA data show about 7.4 percent already showing some entecavir-resistant mutants, although only about one percent caused a rise in the DNA level. But overall I think I am pretty favorable on this drug.

DR. ENGLUND: Dr. Seeff?

DR. SEEFF: I agree that this is a very good drug. This is a bad disease and we need treatments. We have three other treatments and I think that this drug has some advantages that the others don't have, namely at least at this point, the lower rate of mutant strains developing and no different toxicity. There is the potential of malignancy and I think that that is an issue that needs to be addressed, but I think that in the context of where we are I believe this is a good drug, worth supporting and should be used.

I do believe that the concerns that have been expressed, even though there is some information that has gone some way to allay my

original anxiety because I was really concerned about the malignant potential, I do think that, obviously, the pharmacovigilance studies that have been suggested are critically important and need to be done, looking both for outcome with respect to malignancy and to the issue of the development of mutagenic strains. So, I agree that I would support the approval of this drug.

DR. ENGLUND: Dr. Munk?

DR. MUNK: I agree that this drug appears to represent a significant addition to the armamentarium against hepatitis B. One of the factors that impresses me is the lack of interactivity with HIV medications, the fact that there is no cyp3A involvement which should make it easier for a physician to prescribe in a co-infected patient.

I guess I am concerned about the implementation of the long-term follow-up study. I have some concerns about that for carcinogenicity and I am assuming that there will be inevitable clinical follow-up of emergence of resistance

mutations as there has been for every other antiviral drug.

DR. ENGLUND: Dr. Haubrich?

DR. HAUBRICH: The risk-benefit for any drug is clearly dependent upon the disease being studied. If entecavir was an anti-retroviral that had 7 logs reduction with little development of resistance by 48 weeks we probably would all be home now.

[Laughter]

Even accounting for the fact that it is 2 logs better than a previously approved drug, you would have the same conclusion. So, I think that the efficacy data, the safety data, the resistance data, although I might characterize it perhaps a little bit differently, clearly show the drug has great activity, and the only negative, the only thing that is even a question at all is these animal data. So, given the need for further therapies for hepatitis, as well as the greater demonstrated efficacy, I think a plan of use of the drug with careful monitoring should be done. When

we get to the questions about monitoring I will have some comments on that.

DR. ENGLUND: Dr. Bartlett?

DR. BARTLETT: As an HIV clinical investigator, I have a few comments. I am impressed that the safety of this drug is similar to lamivudine. I am impressed that its antiviral efficacy is better than lamivudine. In the short-term the resistance appears to be less than with lamivudine. I think there may be an opportunity here with lamivudine-resistant virus to look at some of the challenges in treating those patients, and it may be that in that arena some form of combination therapy for hepatitis B may be necessary.

I am still a bit uncertain about interactions between anti-retroviral drugs and entecavir. It appears, based on in vitro studies, that there shouldn't be any problems but the proof of the pudding is always what happens in patients, and I will be keen to see what happens in co-infected patients as that data set matures.

The context of the animal carcinogenicity data is reassuring and I am reassured to hear Dr. Farrelly's comments. I think the proposed

pharmacovigilance study is reasonable although there are a lot of details that remain to be worked out, and I think it would really be crucial to have diligent follow-up of those patients in order to achieve the desired goal.

DR. DEGRUTTOLA: Victor DeGruttola. From the information that has been developed to date, the risk-benefit profile of entecavir appears very favorable. The issue has been discussed about uncertainty regarding future risk of malignancy. So, it will be important to discuss and develop an appropriate plan to evaluate that risk over time.

DR. ENGLUND: Mr. Grodeck?

MR. GRODECK: As a person who wakes up every morning with the very real threat of liver cancer, I think that the risk-benefit of entecavir right now is positive. It is a hypothetical cancer threat of the future and a very real threat of liver cancer from the virus itself. Now, ten years

from now will I feel the same way? It is unknown but today, given the drugs that are out there, I think the benefits outweigh the risks.

DR. ENGLUND: Dr. Wood?

DR. WOOD: I would have to concur with the comments of all of my previous colleagues regarding the favorable risk-benefit profile for this drug regarding specifically the efficacy, clinical safety and the resistance data. Given this signal that has been detected in preclinical animal model carcinogenicity studies, I do think that we have to say that that signal is significant. I do think that the sponsor's explanation of the signal attributed to pulmonary tumors in mice is satisfactory.

My major concerns are that since this signal is significant, we do know that it is impossible and it is unknown as to how this significant signal may translate into a clinically significant risk or hazard. So, since the risk is unknown and can't be known, my major concerns are being able to detect excess non-HCC malignancy, if

it occurs, as soon as possible, which really relates to the post-marketing study and monitoring.

The second issue is something that we have not discussed really, and that relates to the duration of exposure to the drug. Since presumably, if there is increased risk associated with exposure to the drug--I don't really have a sense or a handle on how long people are going to be treated. And, if it is a recommended period or if it is indefinite the presumption would be that if the exposure is going to be very, very long it might carry with it an increased risk. So, that is an issue if we can address possibly that I would like to try.

DR. ENGLUND: Dr. Paxton?

DR. PAXTON: I just want to add my thoughts. As an HIV epidemiologist, I am more accustomed to thinking on the population level and I am impressed by what I have seen today about the potential of cost benefit analysis for this drug, particularly given the limited options that are currently available to us and the strong efficacy

results from this drug.

In my mind, and I think in the minds of other people, there really is no other way to resolve this issue of the potential malignancies except to do the post-marketing vigilance study. So, it is going to be in our best interest to make sure that that is done to the best possible standards within the limitations, like the possible crossover of drugs during the study. But my general comment is that I think I would recommend approval for this particular drug.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I am not going to echo what has already been said. I will focus my comments on resistance. I agree that the risk-benefit profile is positive in all aspects of what was in question 1. I think the company is to be commended for the thoroughness of the available data to date but, as I mentioned earlier as a cautionary note, given its superb potency and its durability of response over such a long time, I think we have an incomplete resistance story and I think follow-up will be

needed in both the treatment-naive and the treatment-experienced subjects to really understand what the resistance pathways are for this drug. We know that if we were meeting in two years and we were presented data sets of the virologic breakthrough at the highest baseline HBV subjects, the company would have that data set and we will be eager to see that in their vigilance surveillance of drug resistance, and we encourage them to keep putting out the data. Thank you.

DR. ENGLUND: Dr. Sherman?

DR. SHERMAN: First, I would like to also commend the sponsor of this drug and the agency for their detailed and thorough analysis. As a hepatologist, I think this drug will add significantly to the tools we have available to treat patients with liver disease, and overall the risk-benefit ratio is clearly in favor of moving forward with approval of this drug, particularly in the e-antigen positive and e-antigen negative naive population. I think that it will probably come up under the question of the role of this drug in

terms of the lamivudine-resistant population and the best way to manage those patients, and that discussion will follow.

DR. ENGLUND: Dr. Herbert?

DR. HERBERT: I am a veterinary pathologist and my expertise with the National Toxicology Program is in rodent carcinogenicity studies so my comments are going to be based on that expertise. I agree, and I want to applaud the applicant. The rodent studies were thorough and well conducted. Although the drug seems to be carcinogenic at several sites, I think that the carcinogenicity is shown at multiples of doses that are significantly higher than in human exposure. In my estimation, based on those results, I think the benefits of this drug outweigh the risk and I would be in favor or approval.

DR. ENGLUND: Thank you. Dr. Fish?

DR. FISH: As a clinician and clinical researcher who takes care of HIV-infected individuals, many of our patients are co-infected with hepatitis B and hepatitis C, as you know.

This is a disease that does have and can have devastating consequences, including the significant potential for malignancies which is a reality for these folks on a daily basis. I think that the breadth of the trial data that was presented was very impressive and highly convincing. Certainly, the 7-log drop that Dr. Haubrich mentioned is quite impressive. The breadth, in terms of its multinationality, the differing populations that have been studied and studies that are ongoing, I find impressive.

Also, I think the collaboration, the briefing document--and I wonder about that name; they are not so brief--have lots of good information where there was obvious collaboration, back and forth between the sponsor and the agency that really seemed to culminate in having a good product in the end. So, in my opinion the risk-benefit ratio is favorable, highly favorable.

DR. ENGLUND: Thank you. Dr. Washburn?

DR. WASHBURN: As an antifungal investigator, I am a fish totally out of water--

[Laughter]

--but I do have ears and I have been listening carefully all day, and my response is

that the risk-benefit ratio appears acceptable, and I will be looking forward over the coming years to learning more about drug interactions, a topic on which we haven't heard much today.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: Yes, I am a clinical pharmacologist as well as a clinical infectious disease specialist, and I think this drug, in terms of nucleoside analogs, has an extremely favorable risk-benefit ratio. I was quite impressed with all the data.

Unlike Dr. Bartlett, I am much less concerned about drug interactions. The in vitro data seem extremely convincing that we shouldn't be expecting drug interaction with HIV drugs. Overall, I think if you look at other nucleoside analogs--famciclovir as an example and ganciclovir--that have tumor producing properties, I think this drug actually performs better overall.

So, I feel that this is very favorable.

DR. ENGLUND: Dr. Sun?

DR. SUN: Actually, I thought that the answer to this question is best stated by a single sentence in the FDA briefing document on page 22, which I was just going to read, not that there weren't other good sentences in the document--

[Laughter]

--it says, "these positive findings from the entecavir studies must be weighed against findings that are less clearly understood." I think you will notice the word "risk" does not appear in there and I think this is carefully worded to indicate that what we are talking about that is of potential concern is a finding that is of questionable clinical relevance. I think the benefit of the drug is very clear. It is a very clear and very clean win in all the studies they have done. It is clear in a disease with high morbidity and high mitochondria. But the answer to the question, unfortunately, can only be answered by the kind of post-marketing surveillance study

that they have decided to undertake, which I would say is a very significant undertaking but, unfortunately, there is really no other way to answer the question.

DR. ENGLUND: Thank you. Before I summarize, are there any questions or additions from Dr. Schwarz or Dr. Bell?

DR. BELL: No, I pretty much agree with what everybody has said. The one small point I would make is on the topic of the various patient populations that have been studied, which certainly is a very extensive study but just, for example, to remind people of Dr. Lewis' point about the very small proportion of African American patients in these populations. I am sure there are a lot of potential explanations for why this might be the case, but it is something that I think we don't want to forget about and perhaps will need to be dealt with as we go forward.

DR. ENGLUND: Well, thank you, everyone. If I may take the prerogative of just doing a brief summary, and then we are actually going to put this

to a vote for question 2. But to summarize, I think I have heard quite universal opinion that there is a favorable risk-benefit for the drug entecavir. The enthusiasm perhaps is relatively high. There remain concerns about resistance, well-founded concerns and well-founded concerns about details of the pharmacovigilance study which I think we are going to be able to address later on this afternoon.

I think that we all have appreciated the input on the carcinogenicity story from both the FDA and from Dr. Herbert also. It is very good to have more input in this as many of us, clinicians, don't have expertise in this, and it is reassuring to hear similar stories from the company, the FDA and from our own independent person here.

As was stated by our--what are you? Civilian representative?

MR. GRODECK: Patient representative.

DR. ENGLUND: I think that we are dealing with very real risks of hepatitis B. I see the patients. If we don't see the patients, some of us

are evaluating the numbers and looking at the outcomes of these patients and the very, very real risk versus theoretical concerns which do need to be followed up. I hear there are cautionary notes concerning resistance and concerning how we are going to do post-surveillance, but that overall, as a group, we are finding quite good benefit of this particular compound.

So, that is what I have heard as a group. At this point I would like to move to question number 2, and this part is only for the voting representatives, which is most of us. I am just going to call you off in the order that you are listed, and I don't know what order it is but it is nothing personal. Dr. Gerber? You need to say yes or no.

Question No. 2

The question is, number 2, does the risk-benefit assessment for entecavir support the approval of entecavir for the treatment of chronic HBV in adult patients? And you are allowed to answer yes, no or abstain.

DR. GERBER: Yes.

DR. ENGLUND: Dr. Washburn?

DR. WASHBURN: Yes.

DR. ENGLUND: Dr. Fish?
DR. FISH: Yes.
DR. ENGLUND: Dr. Herbert?
DR. HERBERT: Yes.
DR. ENGLUND: Dr. Sherman?
DR. SHERMAN: Yes.
DR. ENGLUND: Dr. Johnson?
DR. JOHNSON: Yes.
DR. ENGLUND: Dr. Paxton?
DR. PAXTON: Yes.
DR. ENGLUND: Dr. Wood?
DR. WOOD: Yes.
DR. ENGLUND: Dr. Grodeck?
MR. GRODECK: Well, I am not a doctor but I would still vote yes.
DR. ENGLUND: Dr. DeGruttola?
DR. DEGRUTTOLA: Yes.
DR. ENGLUND: Dr. Bartlett?
DR. BARTLETT: Yes.
DR. ENGLUND: Dr. Haubrich?
DR. HAUBRICH: Yes.
DR. ENGLUND: Dr. Munk?
DR. MUNK: Yes.
DR. ENGLUND: Dr. Seeff?
DR. SEEFF: Yes.

DR. ENGLUND: Dr. So?

DR. SO: Yes.

DR. ENGLUND: Dr. Schwarz?

DR. SCHWARZ: Yes.

DR. ENGLUND: Dr. Bell?

DR. BELL: Yes.

DR. ENGLUND: And I am Dr. Englund and I am going to vote yes, and that makes it a unanimous vote so we do not have to address question 2B so we have already eliminated some of our work.

Question No. 3

For question 3 I would like to have a little bit more discussion, particularly from those people who have the expertise. We have kind of addressed this already but I would like to formally answer the question.

Question 3A states, if the answer to number 2A is yes, which it is, discuss whether the results of the rodent carcinogenicity studies should impact the indication and usage section of product labeling.

That is 2A, and 2B is discuss the potential role. But I think question A really is important. I guess I would ask first from the FDA if you could explain does this mean either a black

box or a warning? Could you explain specifically what you want?

DR. BIRNKRANT: I will clarify that question. What we were interested in was, given that the presentation appeared as though the drug was being presented such that it would be first-line therapy, given the findings of the animals, we wanted somewhat of a discussion on whether or not the committee would consider anything else other than a first-line indication. We specifically asked about indications in the usage sections of the product labeling. We can talk about other sections of the labeling as well

but first I would like to address the indication and usage section which we can expand with additional information that will be helpful to practitioners with regard to use of this drug in various populations.

DR. ENGLUND: So, this first part is indications and usage and then the carcinogenicity could actually be a little discussion.

DR. BIRNKRANT: Right.

DR. ENGLUND: I would like to ask some of our hepatologists to comment first on this, if I may.

DR. SHERMAN: There are two of us.

DR. ENGLUND: Good.

DR. SHERMAN: I think that the drug should be labeled for first-line therapy, and I think that it will be an important addition for the treatment of those patients. The carcinogenicity listings and what should be put into that label--I think that a black box warning is not indicated at this stage, based on what type of reporting has been used for other drugs. Until we see a clinical

signal of some sort in humans, or at least a primate, it is not a reason to go ahead and issue a specific warning in that regard. All of these patients need to be monitored for malignancy, particularly hepatocellular carcinoma, and I don't know if the label is the place to do that but that certainly should be part of the standard of care of the management of patients with chronic hepatitis B infection.

The patients that have lamivudine resistance, which means second-line therapy, I think represent a group that I would turn and ask first the agency and then the company to provide information about comparisons with other available products in terms of efficacy prior to stating that that is a group. It is clearly safe; it is clearly efficacious relative to lamivudine but is it the best first-line therapy or second-line in a sense that the patients who are lamivudine-resistant already have been on lamivudine.

DR. ENGLUND: Dr. Seeff?

DR. SEEFF: I agree with Ken that this

should be labeled a first-line drug. I do think though that there should be mention, not in a black box, of the fact that studies have shown that there has been development of cancer in animals, and I think it is fair enough, if it possible to do this, to discuss the issue that this is at a much higher dose than one would normally use and there is little concern. But the other side of the coin is that, in fact, this drug may lower the rate of liver cancer by, in fact, reducing disease progression and may be beneficial with respect to liver cancer and not harmful. But I cannot see that there could not be at least mention of this in the insert but I don't think a black box is needed.

DR. ENGLUND: I am going to call on people unless people want to volunteer. Dr. Bartlett?

DR. BARTLETT: Well, certainly I would agree that it seems that it is indicated for first-line treatment. I would share Dr. Sherman's question back to the agency about second-line treatment, whether it needs to be compared to adefovir or tenofovir to have that indication. But

I agree with the comments previously made.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: I also agree with everything that has been said. This should be a first-line treatment. I think in most viral diseases-and I have a lot of experience treating HIV--we try to use the most effective therapy that doesn't result in resistance and this seems to be the case right now for all the drugs that are available. So, I think it should be first line.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I agree with the first-line label. I think, as was written in the materials, we saw data presented for second-line indication versus lamivudine and other drugs out there. So, I think the agency and sponsor should be encouraged to further study second-line therapy in comparative studies; combination drugs, because of the likelihood of emergence of further resistance across resistance within the nucleoside class but, clearly, first-line therapy could be put in the label.

DR. ENGLUND: Dr. Haubrich?

DR. HAUBRICH: Well, I was going to play devil's advocate and say that, in fact, the best

efficacy, although in smaller numbers, is with patients that have lamivudine failure. If you are looking at the risk-benefit, people that need it the most have the most benefit so any potential risk from cancer is lower.

On the other hand, I think that arguments from members of the committee have convinced me that that risk is fairly low so I would then agree with the first-line indication and I probably would say that it has shown good efficacy in second-line failure as well and would not restrict it based on that. So, I would probably allow both.

DR. ENGLUND: Dr. Wood?

DR. WOOD: I concur that there is clearly an indication for first-line therapy. I also agree that there appears to be very strong evidence for its efficacy as second-line treatment. I do think that in the indications and usage one of the phenomena that occurs is that once a new drug is

licensed and approved and it is highly potent--7, 9 logs is head-spinning for many individuals so there is a tendency to put individuals who are the sickest and rush them to the new agent and I think there would need to be some comment about the fact that individuals with decompensated liver function actually had higher SAEs than individuals with compensated liver function. So, there would be that kind of precaution in the clinical sphere. I also agree that based on the FDA's historical data about what has been done on a case-by-case basis for ganciclovir and other drugs the carcinogenicity signal that came from the animal studies does not warrant a black box warning.

DR. LEWIS: Janet, could I answer some of those questions to the FDA?

DR. ENGLUND: Sure, Dr. Lewis.

DR. LEWIS: The question was asked about comparisons in second-line therapy after lamivudine failure. The one thing that I can say is that if you look at the current adefovir product label there is a very small study in

lamivudine-refractory patients that is listed in that label. The endpoints were not really similar and it is hard to do cross-study comparisons but the study that Bristol-Myers Squibb has completed is a much larger study and looked at a good number more endpoints, including histology. So, there is the evidence that was presented today in the 026 study that would support that kind of an indication.

The other question that came up about alternatives to putting in carcinogenicity data, almost every product label that is issued has a section that is devoted to carcinogenicity and mutagenicity. What those sections do is they describe the findings in the studies with the ranges of multiples over which the studies are conducted so that you can determine whether it is very close to the human dose or many, many times the human expected exposure, and puts it in some context without trying to make a correlation to a particular human level of risk. So, that is kind of a given for any of the drugs that come out of

our division.

DR. ENGLUND: Thank you for the clarification. Dr. Munk?

DR. MUNK: Yes, just picking up on the last comments in terms of the label and the discussion of carcinogenicity, I would urge the agency to go a little bit further in terms of putting those comments and data in context so that, beyond a recitation of the data from the existing studies, perhaps there could be a statement of the CAC findings; perhaps there could be a statement, as was made here, that clearly this is a patient population for whom monitoring of emerging cancers and tumors is standard of care. I am concerned that some physicians and certainly some patients reading it either will be too reassured by the multiples of human dosage and simply ignore the risk or, on the other hand, given the number of column inches devoted to it, will be concerned about it. So, I would just like to see more context rather than less.

DR. ENGLUND: Dr. So?

DR. SO: I pretty much agree with all that has been said. I think it should be approved for first-line treatment. I also agree the insert

should have something mentioning the risk of rodent carcinogenicity. I think, you know, the data actually shows also that it could be effective in cases of patients who are lamivudine-resistant, although, you know, since we don't have any uniform outcome assessment we really can't compare whether it is better than adefovir. You know, there is really no data to compare.

DR. ENGLUND: Dr. Fish?

DR. FISH: I would agree with the first-line indication and also would agree with the second-line indication in the treated population that was presented for these three pivotal trials, the lamivudine-treated individuals as second-line therapy. The others, the studies and work is ongoing. I would also agree with the comment in terms of future studies and looking at combination therapies of some of these drugs, and I think that has a bright future.

DR. ENGLUND: Any other person who hasn't commented? Dr. DeGruttola?

DR. DEGRUTTOLA: I would just comment that I agree with the indication for both first-line therapy and second line for lamivudine failures, and also with the FDA's discussion about how they

handle the carcinogenicity information.

DR. ENGLUND: I would actually like to call on Mr. Grodeck to make sure that we have your opinion too.

MR. GRODECK: Well, I think I always have something to say here. Right now it seems the benefits outweigh the risks, today. I am thinking to myself where will I be in ten years. I will have survived the risk of liver cancer and where I don't want to end up is that I get lung cancer ten years from now. We encountered the same problems with HIV. You eliminate a lot of the risk from the virus only to see emerging--I guess it is called co-mortalities [sic]. So, I guess I want to see some mechanism, some strong mechanism that goes into place and holds accountable the reporting

system so I am aware, as a patient, that I am taking this risk because I am afraid after it is prescribed, you know, while we have suppressed the virus and go on about your day, but I think what we will probably see is an increase, slow but steady increase of cancer over time, cancer risk. So, I just want everyone to be thinking long term.

DR. ENGLUND: Thank you.

DR. BIRNKRANT: As was mentioned, we have a section in our labeling for carcinogenesis, mutagenicity findings and impairment of fertility so, in addition to putting wording in that section, which is an obvious section to place wording although it may not be the section where physicians tend to go to when they are reading labels, it is possible to put it in another section of the label, perhaps in the precautionary section and then we can always refer treating physicians to the carcinogenicity section of the label as well. But I agree with what was said, that it doesn't really rise to the level of a boxed warning.

DR. ENGLUND: Have we answered your

question 3 to the satisfaction of the agency?

DR. BIRNKRANT: Your discussion has been quite helpful.

DR. ENGLUND: Great!

DR. BIRNKRANT: There is 3B though.

DR. ENGLUND: Well, we kind of discussed--

DR. BIRNKRANT: A little bit.

DR. ENGLUND: --but let's more formally discuss 3B. We pretty much discussed 3B.

[Laughter]

The potential role of entecavir in the treatment armamentarium--I think we had several questions which were discussed with a little bit of a difference of opinion. I think there was universal acclamation for this drug for the treatment of HB e-antigen negative and positive. That was uniform. The question was whether this committee felt that there was sufficient data in indications for labeling it for lamivudine resistant or not naive patients. There was a little bit of waffling and then I think Dr. Lewis gave us a little bit of background too. But I

think that is something that we could discuss a little bit further. Yes, Dr. Paxton?

DR. PAXTON: Again as a non-hepatologist, actually I found the data for the lamivudine-resistant, the effects in that group, to be pretty striking so it appears to me that this would be--I don't know how it compares to adefovir but it looked pretty striking, what was presented today, so I would say, from what we saw, that it would be recommended for treatment of lamivudine-resistant HBV.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: No, I agree that this drug should be approved for lamivudine-resistant HBV virus as well. Based on what Dr. Lewis said, I mean, it seems to be that we have more data. It would be great to get a comparative study with adefovir and entecavir but we don't have that and it seems to be that we have a wealth of data on lamivudine-resistant virus so I think it needs to be approved for both indications.

DR. ENGLUND: Dr. Bell?

DR. BELL: I am not a clinician and pardon my ignorance. Is adefovir labeled for treatment of lamivudine failures?

DR. LEWIS: Yes, it is, and I would like to remind the committee that, while we didn't discuss the data today, there is an ongoing, still enrolling study, comparing adefovir and entecavir. These are very advanced patients. They are patients with decompensated liver disease. What we may not have for quite some time is any data comparing entecavir and adefovir in less advanced patient populations in first treatment failure or treatment naive patients. But there is more data coming and we are expecting that data to be very useful.

DR. BELL: I would just say that it seems to me that the level of information that we have about how entecavir behaves in patients who have failed lamivudine is better than the data that we have for adefovir and that, therefore, whether we are completely satisfied with all the data is perhaps a different issue than whether it rises to

the level of meriting labeling for that indication.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I don't think we were waffling. I think we all agreed about the second-line therapy and I don't want my earlier comments of desiring the studies that Debra just mentioned to cloud that. I personally thought that second-line data was beautifully presented and sufficient for that label. But, again, I would love to see in the studies they have mentioned further studies of earlier stages of treatment experienced patients and further development of drug resistance profiles and cross-resistance profiles in patients so we better get a handle on that because I still think we are headed toward combination therapy based on what we saw this morning. Thank you.

DR. ENGLUND: Thank you. I think that clarifies that. I don't think we need to go around the table to get everyone's opinion unless Dr. Birnkrant wants that.

DR. BIRNKRANT: No, that is fine. I am

satisfied for now.

[Laughter]

DR. ENGLUND: If she is happy perhaps we can move on. Does anyone else have any questions on question number 3? I guess I would like to add one statement. As a clinician, I want to be able to use entecavir in my lamivudine-resistant patients and for that I need labeling because I am dependent on getting reimbursement and things like that. So, I really think that it is going to be done. I think they have good data and I would support that.

Question No. 4

Question number 4--aha, Dr. Schwarz, you are still with us! this question is specifically addressing the issues with pediatric patients and Dr. Wood is a pediatrician too. The question states assess the potential risks and benefits of proceeding with development of entecavir for the treatment of chronic HBV in pediatric patients. Part B, what, if any, additional information is needed in order to proceed?

DR. SCHWARZ: Well, first of all, I would like to express my gratitude for inviting a pediatrician, and I am honored to be the

pediatrician to try to give the most balanced assessment I can of what I believe is a very important problem.

So, in terms of the risks, I think we understandably are extra conservative when it comes to giving any drugs to children. We do need more data on carcinogenicity potential before we proceed too much further, and I was interested to learn that the so-called lifetime animal exposure studies started with teenage rats and, as I will try to articulate, there are reasons to consider treating hepatitis B in fairly young children. So, I think it would be important to do some more studies in post-weaning rodents and, in particular, young primates.

I am not a molecular biologist but I am worried that this drug is not an obligate chain terminator. So, the possibility of site-directed mutagenesis is something that I at least need to

raise. I also wonder about the risk of exposure to ovulating females. I thought I heard that it was not integrated in mitochondrial DNA and that there was no risk of lactic acidosis but I would just like to make sure that I understood that correctly.

Then, of course, another risk that is unknown is the risk of long-term exposure to the injured liver. It was interesting to me that almost all of the toxicology and carcinogenicity animal studies were done in animals with a normal liver, whereas patients with hepatitis B, including even young children, have an injured liver. I am actually excited about the woodchuck studies in which, of course, the drug is given to animals with an injured liver and it looked beneficial in that regard but I think we need a little bit more data.

In terms of the potential benefits for an addition of a safe and effective hepatitis B drug for the pediatric hepatitis B clinical problem, I think that is an enormous benefit. There are some thousands of children in the United States with hepatitis B, probably falling in two camps, urban

adolescents and also international adoptees, and I should say that the urban adolescents who are probably at the highest risk for the infection have the lowest hepatitis B vaccine coverage. Then, there are millions of children worldwide with perinatal transmission of hepatitis B.

There are two FDA approved drugs for hepatitis B in children. Interferon is approved for hepatitis B-infected children one year and up, but it does have a significant side effect profile. Lamivudine is approved for children three years and up, but as is the case with adults, even at one year of treatment there is a 20 percent resistance rate. And, the pediatric adefovir trials are proceeding at the present time.

So, newborns who have acquired hepatitis B from their mother probably have the highest lifetime risk of morbidity and mortality from liver disease and liver cancer. In some studies it is as high as 40 percent lifetime risk. So, this is a very significant problem.

This has not been said, but there is also

a very significant social stigma of having hepatitis B, including in a young child. This is a very real problem so it is one of the factors that motivates pediatric hepatologists to be eager to identify effective drugs. Parents also are eager to find therapies for their infected children. Finally, there is some data from the interferon studies that it may actually be more effective to treat hepatitis B in young subjects. So, I am very glad to be here for that reason.

Finally, I should say that we might as well be realistic. There is an oral suspension of entecavir for consideration on the table today, and the minute the FDA approves that drug there will be off-label use in children. So, that being the case, I think to the question should there be pediatric development studies, the answer is yes because if there aren't we are just not going to know what is going to happen when young children take this drug.

In terms of the recommendations, I have talked about doing the carcinogenicity studies in

the very young animals, including primates. I am excited about the post-marketing adult studies that are planned, and I agree with the comments that there really has to be built into that effective monitoring for cancers because I think the human carcinogenicity studies we have heard about to date have been in clinically manifest tumors. There hasn't been, for the most part, much screening. Also, I think in studying this large cohort of treated adults, it will be a chance to get reproductive history in a systematic fashion.

If it does turn out that there is an increased risk of cancer long term, as a pediatrician who is always looking for non-invasive markers of cancer potential, I would love at least to see the peripheral blood lymphocytes of the cancer patients frozen so that those DNTP pool studies could be done maybe on a case control basis.

I would like to put up for discussion consideration of holding approval of the oral solution until we have a little bit more

carcinogenicity data from both young animals and the adults. Then, if these studies are reassuring, I would like to argue for doing PK studies in young children and then, finally, the Phase II safety and efficacy studies.

DR. ENGLUND: Dr. Paxton?

DR. PAXTON: I would just ask a clarification question. You are advocating that the approval for the oral suspension be held up simply to guard against the off-label use in children? Is that the reason?

DR. SCHWARZ: I think it should be discussed because there will be off-label use if it is available, particularly given the limited number of alternatives.

DR. LEWIS: Just one comment about the oral suspension solution, that product is being considered in order to be able to dose entecavir appropriately in patients with renal insufficiency, and without the oral solution that won't be able to be done.

DR. ENGLUND: Dr. Wood, I am going to take

the liberty of calling on you.

DR. WOOD: Well, I want to thank Dr. Schwarz for answering one of my questions. I was not aware what the specific risks were for long-term disease progression as far as hepatocellular carcinoma disease in very young children who had hepatitis B. It clearly is significant. I would have to echo all of your comments and the fact that we clearly will need, I do believe, for carcinogenicity purposes animal studies in the neonatal rats up until adolescence to see whether or not there is any excess tumor incidence which would be very important.

Given all the limitations regarding dose, particularly since the drug is 75 or 80 percent renally excreted, there is the need for the suspension clearly and there is tremendous renal co-morbidity in patients commonly who have hepatitis B or HIV and hepatitis B.

I will have to echo though that the urgency to conduct those preclinical animal toxicity studies and then move into pediatric

studies very efficaciously is going to be necessary because when you have drugs that are very potent it is going to be a hot drug. It has a favorable resistance profile. It has a favorable safety profile. We are going to be recommending it not only for first-line therapy but second-line therapy. People will use it in children if there is a suspension without any safety or efficacy data in that population. The safety issues in children and in neonates can definitely be very, very different, and I will put forth the example of a nucleotide analog, adefovir, for the indication of HIV infection. We have seen significant musculoskeletal, bone toxicity in preclinical animal models which has also been seen and observed in human clinical studies. So, that is an argument for pediatric studies to be done promptly.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I am also an HIV treater and I am an infectious disease adult clinician who takes care of a large number of older African Americans particularly men but also women in

Alabama who are on dialysis or near dialysis, who have HIV and hepatitis B co-infection; not many tri-infected HCV, HBV, HIV infected, but I need the oral formulations. I can't always get the patients to pick them up at the pharmacy but we won't go there. But I need all formulations of this compound once it is approved for adult care. Thank you.

DR. ENGLUND: Dr. Bartlett?

DR. BARTLETT: Yes, I just wanted to echo what Dr. Johnson said. The availability of a liquid formulation is really helpful in adult practice, not just for dose titration in patients with renal failure but also for patients who have difficulty in swallowing pills. So, I think having it is really important for adult medicine.

DR. ENGLUND: I would like to interject my feeling as a pediatrician also, Dr. Schwarz. I think one population that is relatively small but that should be encouraged for studies to begin urgently, especially PK studies, is our transplant population. We do pediatric transplants, many of

them in my institution, but we do pediatric transplants with a mean age of nine months. So, many of these children are young. And, if there is an HBV risk we don't even potentially need all the animal studies to be done. If one were to target a target group that you would want to start doing pediatric research on, it could potentially be patients at very high risk which could include transplant patients. Most of them, of course, don't have HBV.

DR. SCHWARZ: I was going to say with all due respect, and I am the medical director of our pediatric liver transplant program, there are very few children in the United States with hepatitis B who have at least a liver transplant; it may be a little more common with kidney transplants. But I still think, all in all, there are many more children who might benefit from the studies and if you had an increased prevalence of a malignancy in a transplant patient--since when cyclosporin was introduced we learned that there was a 100-fold increased risk of all kinds of malignancies, I

think I personally wouldn't want to begin the studies there. I would rather proceed with a more established population.

DR. ENGLUND: Well, I am concerned that we really don't even know how to dose--I am concerned about malignancy but I am concerned the drug is going to be used inappropriately because we don't know how to dose them also.

DR. SCHWARZ: Right, but I wouldn't start with the transplant patients.

DR. ENGLUND: Okay. Dr. Haubrich?

DR. HAUBRICH: Just a quick comment, when I first looked at this question I really had a hard time making up my mind about it, but the discussion by my colleagues here has answered it. Clearly if the oral suspension is needed that will lead to use in kids, it needs to be studied and I wouldn't wait.

DR. BIRNKRANT: So, what we heard then, just to clarify, is that the committee feels as though this could be an important drug for the pediatric population, however based on the animal

findings, they want further animal studies before conducting a formal trial in children. Is that correct?

DR. LEWIS: You know a carcinogenicity study in animals is going to take at least two years.

DR. ENGLUND: I think that was Dr. Schwarz's opinion, and in my opinion, I think that limited PK studies could be done concomitantly with the animal studies--

DR. SCHWARZ: And I agree with that.

DR. ENGLUND: --because I don't think waiting two years to start PK studies--it is not going to work.

DR. SCHWARZ: Right, and you pointed out correctly that the dosing is important in children and the PK may be different, and it would be most different in the youngest subjects.

Then, I did want to ask the FDA a question about labeling issues when it comes to safety in pediatrics since there is no data. I think that most drugs in the Physician's Desk Reference have

not been specifically approved for pediatric use. So, to be honest, I think many pediatricians simply ignore the warnings when it comes to children. But in this case, where at least I think we all agree that the same kind of careful studies that have already been talked about should be done to a certain extent in children, I just wonder if there is some special way to put a warning that people will read and pay attention to that it is not for pediatric use.

DR. LEWIS: I am a pediatrician so I am particularly aware of this issue. When there is no data in a particular age group, whether it is pediatrics or geriatrics, we put that very clearly in the label and say there is no pharmacokinetic data in this age group in the pharmacokinetic section and in the other sections; there is no safety and effectiveness data in this age group. That clearly doesn't keep people from using the drug off-label but we do try to indicate where there is a lack of data.

DR. BIRNKRANT: Then just to clarify one

more time, what we are hearing is that there should be concurrent development, that is, a Phase I study in young children at the same time as animal tox studies looking at carcinogenicity in younger animals. Is that correct?

DR. SCHWARZ: And I also think that planning for a Phase II safety and efficacy pediatric trial can begin. That always takes a while.

DR. BIRNKRANT: So, then we will be expecting protocols from Bristol-Myers Squibb over the next few weeks. Right?

[Laughter]

DR. LEWIS: Maybe in the next few months.

Question No. 5

DR. ENGLUND: With that, we are going to move on to our next question, which I think actually might be the most discussion prone question. Question number 5, discuss the applicant's proposed pharmacovigilance plan to address human cancer risk, including comments on the design of the proposed large simple study.

I think we have already briefly addressed this but I think this is the time for us to specifically say what we, the committee, would

recommend to the agency to request. Dr. Haubrich?

DR. HAUBRICH: I think the biggest risk to this study--well, number one, I think that a randomized study design is the right way to do it and is probably the best study design. Number two though, I think that the biggest risk to this study is either lack of enrollment because people just won't do it--why would they want to be randomized to a drug that has already been shown to be inferior? Or, two, that if they enroll, they enroll and then cross over. So, I think it has to have built in a prior contingency plans if recruitment goals are not met and the design changes or if certain pre-calculated proportions of patients cross over before, again, a certain time period that the study design changes as well so then it just becomes a cohort study which, of course, is less desirable but is certainly better than having no study at all. So that two years

from now we don't come back and hear that, well, we started this study; we got 6,000 investigators and we enrolled 35 patients.

DR. ENGLUND: Dr. Bell?

DR. BELL: Yes, I would like to echo that sentiment and just say a little bit more about it. I mean, I kind of laugh at the idea of calling this a large simple study because it is about as non-simple as you can imagine. I think that while we all believe in the best of all possible worlds that a randomized trial is the best way to address a research question, if it is a randomized trial that can't be conducted appropriately it has the potential to give the wrong answer. For example, this issue of loss to follow-up is not a small problem. For a study like this you are likely to have differential loss to follow-up so that the patients that you lose are different than the patients that remain in the study. I think there is certainly the potential not to detect the endpoints of interest differentially because of the people that have been lost to follow-up.

So, I think there are some potential methodologic dangers in a poorly conducted randomized trial, not from any lack of trying on

the part of the sponsor but because of the logistical difficulties involved with trying to mount a randomized trial of this nature--some of the comments that were just made. So, I think there really needs to be a very careful and quick attempt to determine the actual feasibility of doing a study like this, as good as it looks on paper, and move to something else fairly quickly if it doesn't look like it is going to work.

I think, you know, while these concerns about cancer risk are somewhat theoretical at the moment, it is also true that we actually haven't studied patients on this drug the way it is going to be used, which is over a long period of time, and that is another reason to be very serious about really keeping track of what is happening with other cancers besides HCC, in addition to HCC, in this population.

I also think that we should not downplay

too much the relative usefulness of observational studies and using large databases such as, for example some of these Kaiser databases, to address some of these questions, particularly when we are talking about a relatively rare outcome, and we need to have very large sample sizes and there are places that have existing populations that are relevant, not just in the United States, with very good access to data. For example, these Kaiser databases do have information on treatment and it is possible to ascertain exactly who was treated with what for what periods of time. It is also fairly easy to characterize the population fairly well. I would pick an observational study with a large population that can be well characterized, with good ascertainment of data, over a randomized trial where the sort of feasibility issues are such that the patient population is too small, is biased in a way which doesn't answer the question, or otherwise causes difficulties.

So, although I think we often think about randomized trials as being the gold standard, in

this kind of situation I would encourage the sponsor to think creatively about admittedly observational studies but ones that perhaps we might be able to answer the question.

The only other comment I would make is that I think the availability of vital records and of good vital records is an important thing to think about for these kinds of studies, and not just in the United States, but where one of the outcomes is something which is likely to kill people sooner or later, being able to search death certificate data and tumor registry data and the availability of those kinds of registries and other kind of vital records in whatever country you happen to be working in, and in some of the high prevalence countries they are available, I think would be very useful in terms of really making an effort to try to get at the answer to this question using lots of different ways, other than simply relying on a randomized trial which, as I say, is good study design but if it is not doable it doesn't help us.

DR. ENGLUND: Dr. Fish?

DR. FISH: I agree wholeheartedly with Dr. Bell's comments. It does look good on paper but I

am concerned that if I am an investigator trying to convince a patient to go on the study, knowing what I know and what we have learned about entecavir and its potency and superiority to at least one major hepatitis B therapy, I would be hard-pressed to sell this study I think to my patient. Moreover, if I am the patient and I know what I know, I know what arm I would like to be randomized to.

I am not an expert in study design, but I would agree with the suggestions offered, and even looking at the studies that you have and having a follow-up plan for the five to eight years maybe even some of those patients would be willing to continue to be followed in cohorts beyond five years, ten years, or whatever from the studies that are currently existing and ongoing.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: I am just curious to see what people think about the ethical aspects of

randomizing to an inferior regimen. I think that needs to be discussed at least here because, certainly, I agree with Doug that it would be difficult to convince a patient to go on lamivudine when we know that there is a huge difference in response.

DR. ENGLUND: Mr. Grodeck?

MR. GRODECK: To respond to your concern, I wouldn't go on a randomized study to an inferior regimen. I wouldn't do it. And you are exactly correct, it is a hard sell, one that shouldn't have to be sold. Lamivudine is inferior, period. I think it is wrong to sell that kind of trial to a patient. I would just not do it.

DR. ENGLUND: Dr. Bell?

DR. BELL: Just one additional comment on that point, which I think is an excellent one. You know, the sponsor could be developing historical controls using large databases. Once again, this idea that if it is not a randomized trial it is not worth it I think is something that in this situation we want to get away from. Using some of

these available data and large patient populations to develop historical controls I think potentially might be quite useful because, otherwise, we will be faced with a compared to what question if, in fact, we have a large population of patients that are treated with one drug and the patients that are not are not comparable in many other ways. So, I would once again just encourage the sponsor to think creatively about this and not relying on the kinds of things that we do when we are evaluating the efficacy of a drug for licensure.

DR. ENGLUND: Dr. DeGruttola?

DR. DEGRUTTOLA: I just wanted to comment that I would certainly agree that we wouldn't want to develop a study in which patients were going to be randomized to an arm known to be inferior. But as good as the data on entecavir look, there is only 48-week efficacy data and we don't know about longer-term toxicity even though the drug may be used in the longer term. Of course, we don't know about the longer-term carcinogenicity issues as well.

So, I would be reluctant to characterize too quickly lamivudine as an inferior regimen over the long haul, which is what we are talking about,

since that information remains to be developed. I would certainly agree that observational studies can provide a lot of useful information and it may turn out that only observational studies can be done in this setting. On the other hand, I think we ought to be a little careful about what we conclude.

DR. ENGLUND: Dr. Bartlett?

DR. BARTLETT: I recognize Victor's point completely. I think it is a good one. Another comparator arm could be a nucleotide that you could also look at. One way to encourage people to participate, recognizing that these trials are likely to be done in resource limited areas of the world, is through the provision of free drugs that they might otherwise not have access to. So, you want to make sure it is a scientifically robust study and the comparator arms represent the very best standard of care, and then providing drugs to

the participants might be a good way to motivate them.

DR. ENGLUND: Dr. Wood?

DR. WOOD: I have several comments. I would have to agree that we can't make major statements regarding the superiority of entecavir over lamivudine for the long term. The one issue though is that patients are increasingly very sophisticated and educated and they do know that with any current viral infection resistance is a problem. Given the fact that resistance clearly emerges to a significant level within one year of treatment on lamivudine, I think that that alone, in addition to the other primary endpoint efficacy data which we have heard, may make patients even more reluctant to enroll in a randomized study.

One of the questions that I do have for the sponsor, linking on to Dr. Bell's comments about observational studies, is that we have heard about 049 which is the planned five-year post-treatment observation study. I am interested in knowing what the target enrollment is for that

study; what percentage of patients are receiving chronic ongoing treatment or have all the patients enrolled in this study stopped entecavir?

Then the third issue since, whatever the design is of the post-marketing study, is to detect excess incidence of non-hepatocellular carcinoma, I think there should be careful consideration given to the types of screening tests that will be done and recommended for these cancers of excess incidence, and that would need to be clearly defined, and there are some issues of great debate in terms of what is the best way to do that.

DR. ENGLUND: We will have the sponsor briefly address these issues.

DR. MORGAN MURRAY: I am Dr. Morgan Murray, from Bristol-Myers Squibb. Study 049 is an observational study that is ongoing and we have enrolled about 440 patients to date. We expect to enroll about 1,500 patients. As an observational study, patients off of entecavir therapy might be on other HBV therapies. As a reminder, we also have the 901 study as an ongoing study which is

currently allowing up to four years of therapy on entecavir, and that study is ongoing as well and we have nearly 1,000 patients I believe enrolled in that study.

Also, if I may make one clarifying point about the post-marketing study, we are not specifying that patients will be randomized to entecavir versus lamivudine; it is versus any nucleoside or nucleotide so they can also be randomized to adefovir.

DR. BARTLETT: Does that then mean that if they are not going to receive entecavir the other drugs won't be provided by the study?

DR. ENGLUND: That was Dr. Bartlett.

DR. MORGAN MURRAY: Most randomized study drug is, indeed provided. We haven't made any formal decisions on this, and understand that regulations may vary from one country to the next.

DR. DEGRUTTOLA: Is there any plan for crossover for patients who have failed treatment?

DR. MORGAN MURRAY: We don't have any planned crossover in the studies. Patients are

eligible to enroll if they are starting nucleoside therapy or need to change their therapy. We are not preventing switching however, and we will analyze the switching information, patients who switched differently.

DR. DEGRUTTOLA: Have you given any consideration to guidelines for when to switch, or are you planning to just leave that totally to physician discretion?

DR. MORGAN MURRAY: The intent is that it will be a normal use study so we are relying on the physicians to practice according to the guidelines.

DR. ENGLUND: Does anyone have a specific question for Dr. Morgan?

[No response]

Thank you. Dr. Munk?

DR. MUNK: I find the comments about the design of a randomized trial very important and I think that we are getting more and better data from prospective cohort studies in other areas, and that this is a concept, a design that really needs to be looked into. In the area of cardiovascular risk I

think we are getting some incredibly good data from prospective cohort studies, and we should look at this here because I think there are some very difficult issues about randomization.

The other factor that I think argues for prospective cohorts is the whole definition of long term. I suspect that Mr. Grodeck would like to see long term be considered longer than five years out.

DR. ENGLUND: Dr. DeGruttola?

DR. DEGRUTTOLA: I just want to have a comment about limitations of observational studies. I think it is an excellent idea but we have to keep certain things in mind. Here, when we are talking about doing a comparison between malignancies between two groups we are talking about malignancies of all different types. It is different from a setting where there is one particular outcome that you are focusing on. What you would need in order to make inference from an observational study and then use a historic control is to know that you had controlled for confounders, not just for one condition but for all possible

cancers, and I think that that is a tall order. Now, you may be able to detect very large signals in this kind of approach but what the sponsor said is that they were powering their study to detect quite modest differences in increase in cancer. And, it seems to me that it would be very hard to imagine that you could have sufficient confidence that you had controlled for all confounders when using historical controls to compare to some observational studies to be able to reliably detect modest size effects.

So, while I don't by any means argue against the usefulness of doing observational studies, I think we need to keep some of their limitations in mind. I also understand that there can be some difficulties in trying to mount a randomized trial and there will be crossover and other issues to deal with. But I think that this potential should still be explored, particularly since there are other licensed drugs that are available, because there are certain advantages to a randomized trial that we cannot find in other

approaches.

DR. ENGLUND: Dr. Paxton?

DR. PAXTON: Yes, I just have to agree that I think this is a very difficult decision that we are dealing with right now. As an epidemiologist, I dream about randomized and controlled trials and, you know, whenever possible I like to do them but I admit that we have plenty of examples in the HIV world of people voting with their feet. For example, in post-exposure prophylaxis early AZT trials you couldn't enroll enough people because people didn't want to be randomized.

I think it is quite possible that we may find this going on with this thing as more data comes out, and if the results that we saw today continue where it looks like entecavir is superior to lamivudine we might have problems getting people to agree to randomization.

I just want to bring up one thing. I was made a little bit uneasy by the suggestion, and I don't remember where it came from, about one way to

get people to agree to a randomized trial is providing the drug free. I think that that has ethical problems with it, you know, because of the prescriptions against undue inducement for these things. So, I think that is something that we would have to take a really hard look at because I don't know that that in itself would be considered to be following ethical norms.

DR. BARTLETT: Yes, Dr. Paxton, I made that comment and maybe I can answer you. I very importantly prefaced it by saying that all the arms need to reflect the highest standard of care. But there are some populations, especially as you think about the geographic distribution of hepatitis B infection, who don't have access to any treatment and for whom all of this discussion is irrelevant. If they can get access to treatment in the context of a clinical trial, I think that is a positive thing.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I have just a logistic question for the agency about the reporting of the

pharmacovigilance plan. Would a clinician--after seeing the package insert, and in this current climate of scrutiny of post-marketing safety, where could we find these results? Will they be posted on a web, or do they come back to you as a package? How does this get reported back and presented to the general clinicians?

DR. LEWIS: In general there are regulations for post-marketing reporting that apply to every approved drug. What Bristol-Myers Squibb has proposed is sort of a beefed up version of what is required for every drug. We have asked them to do analyses looking at sort of rates of malignancies as they develop and rates of other critical events in hepatitis B on a six-monthly basis, and those would come in to the review division for evaluation by our statisticians, clinicians, microbiologists, etc.

If there is nothing of particular note, probably it would not be posted any particular place. If some trend was noticed, then that might trigger something that might lead to different

labeling or to a "dear healthcare provider" letter, or some other method of communicating the results to the general public.

DR. JOHNSON: So, basically no news is good news?

[Laughter]

DR. LEWIS: That is probably the best way to put it. But, you know, we are also still working with mechanisms of how to provide better communication of ongoing safety evaluations to the public and, as has come out in recent discussions of other products, we are trying to be more transparent about those discussions rather than less.

DR. ENGLUND: Dr. So, you had a question?

DR. SO: I would like to raise a different point. As a liver cancer specialist, you know, one of the issues we have here is trying to also monitor the incidence of HCC in this post-marketing study. So, I think it is important that the sponsor really standardizes the test used for screening on enrollment into the study, screening

for HCC, because if you just use ultrasound, you can miss like 20 percent of the liver cancers. If you use AFP you probably miss 50 percent of liver cancer. So, currently the best test is triphasic CT scan. You know, whatever method you are going to use for screening at the time of enrollment into this study, it really needs to be standardized.

DR. ENGLUND: Dr. Bell had a question?

DR. BELL: I did have a question actually for FDA. I agree with what Dr. DeGruttola says about the benefits of a randomized trial, and I wondered is there a mechanism for FDA to determine or make some kind of assessment of whether this randomized trial is actually working? In other words, is it going forward as one would hope, such that if all of the various concerns that have been expressed about the feasibility and difficulties potentially with mounting such a trial, if that sort of assessment could be built into this so that if there is a need to do something else or shift gears it can be identified in some fashion?

DR. LEWIS: Again, there are regulations

in place for any approved drug. One of the things that is required is an annual report of all ongoing studies so enrollment targets, things like that, are reviewed annually. You may have kind of skipped over this in the company's slides but there is also discussion of having independent data safety monitoring boards to review these data when they get to certain levels of patient exposure. So, you know, when the details get worked out as to whether it is every 5,000 patient-years or 10,000 patient-years, or whatever, there will be an interim analysis so, yes, that can all be built into the study and to the reporting.

DR. ENGLUND: I would like to ask the sponsor if, in your opinion, your proposed study design for pharmacovigilance is feasible.

DR. MORGAN MURRAY: I will try to address that. I will also ask Dr. Pierce if he would like to comment further. We do have a large experience in conducting large clinical trials and have lots of tactics that we have used to enhance enrollment and to enhance follow-up so that, while we may have

attrition, the patients won't be lost to follow-up. We realize this is a very large study and we realize that there could be some difficulties in enrolling and we will, obviously, stay on top of it and implement strategies to facilitate enrolling as quickly as possible. Dr. Pierce, anything else you would like to add?

DR. PIERCE: Just a few points on this, one, the direction I think our pharmacovigilance is actually moving towards is large simple safety studies and we have been encouraged by the agency to pursue exactly this type of design. So, I think there is confidence in the universe of pharmacovigilance that this is the correct way forward and that these are feasible.

Perhaps the agency knows more studies than I do, but Pfizer is undertaking an 18,000-patient study. It is not a randomized study but observing people on a therapy for specific safety endpoints. That is one.

The second point actually regarding some of this is that the success of these trials often

is related to their simplicity. You don't want to weigh them down with a lot of diagnostic testing. BMS would like to answer those in a more nested fashion, the types of things of CT scans and things like that, but the real success of these is often built into not involving the patient with multiple visits and multiple diagnostics.

The third point is that this is a common disease and it is particularly common in developing countries where much usage of the product will be. That is where we would plan to conduct a lot of the enrollment of the study really, where the disease is. So, the conclusion to that was, yes, we believe it is feasible.

DR. ENGLUND: Thank you. I think that is actually very helpful. Before you leave, I just have one other question. Would smoking be a variable? I know it is supposed to be simple but we did hear from our advisory committee on carcinogenicity about the concern potentially of smoking as a co-factor.

DR. PIERCE: We do not plan to stratify on

smoking but we will collect a detailed questionnaire on smoking so will analyze our data on smoking history.

DR. ENGLUND: Thank you. Dr. DeGruttola?

DR. DEGRUTTOLA: I just have one quick question about design. I understand the value, and agree with the value of making it as simple as possible, and I understand why you don't want to have specific guidelines regarding a crossover. But one concern is that in a study where you are trying to show that really there is no difference between two arms, when you have crossover it tends to bias things in the direction of there being no difference. So, I just wanted to recommend for consideration some kind of set of potential guidelines for when to cross patients over if people believe that that is likely to happen, not that those guidelines would have to be followed or that all the tests would be required, and so forth, but potentially consideration for some advice.

The purpose of that would just be to understand a little bit better what the triggers

were that led to switch because that kind of information could be helpful in doing later analyses where you try to tease out the effect of being on one drug or another, not being randomly assigned to one or another but actually having taken the drug in question. So, I would just request consideration of some kind of document describing current medical advice, knowing it won't be completely adhered to but might help reduce the noise a little bit. I would just ask whether people think that is something that could be considered.

DR. ENGLUND: Are you asking the company?

DR. DEGRUTTOLA: Yes.

DR. ENGLUND: We are asking the company.

DR. MORGAN MURRAY: Dr. Bozzette, would you care to comment, please?

DR. BOZZETTE: Sure. Hi. I am Sam Bozzette, from the University of California San Diego. I am advising the company on this aspect. Although the company is designing the trial, I can say that they have not designed it completely and

they are very flexible in terms of wanting to do the best study possible.

In terms of what we are talking about, switching, I think there are two aspects to the trial to be considered. One of them is that one wants to know whether or not the animal data translates into a difference in human cancers. For that, I couldn't agree more with Richard and with Victor that the crossover is going to be a problem because it is going to mix up the time of exposure. But in that circumstance one could look at it as an observational study. They are going to be having 67,500 years of patient follow-up. If you have the initial randomization and you have some reasons why people switch, there might be an opportunity to not only look at the on-treatment events but to try and unravel some of the reasons why people switched and try and correct some of the biases that are associated with those simple on-treatment analyses. There is a variety of techniques that many people on the panel know better than I.

On the other hand, there is really no

other way to get at the pragmatic question of what happens when you choose to prescribe one thing versus another thing with all of the myriad of factors, other than randomizing people. That very pragmatic question, what is the stream of events and outcomes in terms of not only noon-hepatic cell carcinomas but hepatic cell carcinomas and cirrhosis and, in fact, the ability to tolerate the drugs and cross over to another treatment. All of those things really can only be seen through randomization. So, I think here a very strong attempt is being made to answer the biologic question and the clinical question in a very strong way.

DR. ENGLUND: Thank you. Dr. Munk?

DR. MUNK: Yes, I am encouraged to hear what Dr. Bozzette has said. At the same time, I want to echo what Dr. Paxton said. Particularly with the knowledge that the company will be developing this product in the developing world, I think we have to be extremely careful with the definition of equipoise which could be very

definition in different countries, in different parts of the world. The provision of free drug could be an unreasonable inducement, kind of overwhelming the decision about equipoise that we might have in the U.S. So, I would just encourage the company to be extremely careful as the trial is designed to address that issue.

DR. ENGLUND: Dr. Haubrich?

DR. HAUBRICH: I want to put Sam on the spot again, if I could. I know you have probably thought of this but obviously randomized is the best way but if that turns to be unfeasible or have the problems that we have addressed, could you use a different observational strategy, more like you did with the HICSA [?] study and use that to try to address a priori some of the potential confounders that you would have with an observational study?

DR. BOZZETTE: Yes, I think that you could use the full armamentarium of techniques to try and sort through the biases involved. But I would hope that it will be possible to accrue this, particularly since we are talking about standard of

care. It may well be that unusual things will have to be considered. I mean, it may be possible that standard of care is even--this is a suggestion--is entecavir in some circumstances. So, one is going to have to be flexible I think in terms of the design. But as long as people are being accrued and being observed in a standardized fashion you really do have a prospective observational study of a pretty hefty size.

So, it seems to me that that is really the default, that the worst you are going to do is to have a very large, worldwide prospective observational cohort. Even if the randomization turns out to be randomization to advice, advising someone to start one treatment rather than the other, you will have a situation a lot like the one that Dr. DeGruttola described for switching, which is that you will have a little bit of a lever to try and pry apart direction versus preference and separate those factors and perhaps reduce bias that way.

DR. ENGLUND: Thank you. Dr. Birnkrant,

would you like even more advice from us?

DR. BIRNKRANT: A really quick question as pertains the pharmacovigilance study, they had proposed a study of five to eight years. Could we just get a quick discussion on the duration of the trial? In other words, should it be what was proposed or should it be longer?

DR. ENGLUND: I would like to ask our statisticians, like Victor.

DR. DEGRUTTOLA: Well, I think the issue always comes down to the value of the information and the feasibility of doing the study. Obviously, long-term information is always useful but getting information in a reasonable amount of time is also important. If one believes that if entecavir is likely to have an impact in inducing a cancer, that impact is likely to be seen within five to eight years, then obviously one can increase the power to detect that study by having a fairly large sample size, which is the case for this particular proposal which allows you to detect a reasonable signal in terms of increased risk.

Now, if the risk of the cancer doesn't increase for the first eight years but increases sometime in the future, then obviously this kind of

study won't be able to detect it. So, I think the question really turns on what biologically is reasonable in terms of the amount of time it would take entecavir to have an impact on the risk of cancer.

DR. BIRNKRANT: So then we may need to reassess at various time points and as we are approaching that fifth to eighth year make a determination whether or not the trial should be continued or not.

DR. ENGLUND: I would just like to add that as this drug gets used in adolescents and down to children five to eight years is not sufficient and, hopefully, we would welcome this drug in pediatrics but I also think that the surveillance would need to be longer in that age group.

DR. BIRNKRANT: We understand that.

DR. ENGLUND: Dr. Munk?

DR. MUNK: I think there clearly are

options other than extending the proposed large simple trial, and I would encourage the sponsor to work with the FDA to look at alternatives because I think several of us would like to see longer-term monitoring, whether it is of pediatric patients or of adult patients, and that doesn't necessarily have to happen within the context of the large simple trial.

Question No. 6

DR. ENGLUND: We are going to move ahead to Question number 6 which, in fact, gives everyone a last chance to address your pet issues. Question number 6 is are there other issues that you would like to see addressed through post-marketing commitments?

I would just like to ask one question of the agency, and that is how are these enforced? In other words, it is a post-marketing licensure but this particular product is absolutely important, we all are agreeing, for advising or recommending licensure based on these proposed studies. How can you enforce this?

DR. BIRNKRANT: Well, the post-marketing commitment requests are public so the public will be made aware of them. This is an extremely

important situation given the discussion we have just had on question number 5 related to the pharmacovigilance study, so we will also be extremely vigilant in attempting to get the data from that clinical trial.

With regard to enforcement, under accelerated approval regulations post-marketing commitments are mandatory. Under a traditional approval type of approach, less so. But, nonetheless, they are public.

DR. ENGLUND: Thank you. Dr. Wood?

DR. WOOD: I would like to request that the company and the sponsor seek to collect data about sustained viral suppression so that the duration of exposure could be minimized to the drug. I think the sooner that we get those kinds of answers, whether a certain specified duration of treatment results in significant sustained suppression, would be very advantageous to

clinicians as well as to patients.

DR. ENGLUND: Mr. Grodeck?

MR. GRODECK: This is less of a question and more of a statement or reminder that while viral suppression is nice, the true goal is seroconversion. When you look at all the available treatments it all boils down to a certain low number of people seroconverting, and I just don't want us all to lose sight of the bigger picture because we are selling a lot of drugs to suppress a virus and we are adding in a lot of problems. Interferon actually shows some role in seroconversion, and I just want to remind the group, both the agency and the applicant, that where we are really headed is seroconversion.

DR. SEEFF: I have a question. Where did the name Baraclude come from?

DR. MORGAN MURRAY: Dr. Wilber, would you answer that for us, please?

DR. WILBER: Dr. Richard Wilber. In a drug's development as it is approaching commercialization a name has to be selected. The

name has to be reasonable in terms of the capacity to use it around the world. Our marketers would like it to have some link to something about the drug or the process. A variety of these processes generate long lists of names which then, in the end, have to clear a number of regulatory hurdles both here and around the world. They cannot be too close to other drug names so that there would be a medication error potentially--a whole lot of other processes. The names are submitted to regulatory agencies for vetting, as well as our own legal processes. It is a generally standard process and sometimes interesting names arise from that process.

[Laughter]

DR. ENGLUND: Dr. Schwarz?

DR. SCHWARZ: I just wanted to ask if there are any studies planned in adults with normal liver enzymes. I raise the question because, of course, the approved agents to date--interferon and lamivudine and adefovir--all are at least most effective in patients with elevated ALT. Yet, you

look at the antiviral efficacy and many of us, or at least the pediatric hepatologists, follow large numbers of children with very high viral loads and normal ALT values. So, I just wonder if there is any consideration to a small number adult trial in normal ALT patients.

DR. ENGLUND: Dr. Morgan will answer.

DR. MORGAN MURRAY: We currently don't have any studies planned in HBV-infected patients with normal ALT. However, as we, hopefully, enter the post-marketing phase with the drug we will be talking with investigators and health authorities worldwide to define what additional studies we should be conducting with entecavir.

DR. ENGLUND: Are there any other questions for Dr. Morgan? Dr. Sherman?

DR. SHERMAN: Can you comment on any plans to do specific studies in patients with renal disease, renal dialysis patients, who have chronic hepatitis B? I know you have guidelines for dose adjustment but are there any plans to do specific studies in that population?

DR. MORGAN MURRAY: Dr. Wilber, do you have any additional comments on our proposed studies?

DR. WILBER: I believe, as was pointed out, we have an ongoing, currently enrolling study with decompensated patients, many of whom have renal compromise. We will get a lot of information there. If this is an area of further interest we will be glad to talk to the agency and other investigators in terms of refining that information and making it more robust.

DR. ENGLUND: Dr. Munk?

DR. MUNK: I imagine it is fairly high on the company's list but I would certainly want to see a resistance analysis of virologic breakthroughs on entecavir.

DR. MORGAN MURRAY: In all of our ongoing studies we continue to monitor resistance and rebound.

DR. ENGLUND: Dr. Fish?

DR. FISH: Can you comment, other than in the HIV-infected population, are other combination

studies planned of oral therapies?

DR. MORGAN MURRAY: We don't have any combination studies currently planned but, as I said, we will be discussing studies with health authorities and investigators and that is a logical avenue for us to pursue.

DR. ENGLUND: Thank you. With that, I would like to give a real brief summary unless there are any other final comments from the committee. Dr. Wood?

DR. WOOD: The only comment I have would be to commend both the sponsor and the agency. I think when we had discussions two or three years ago regarding the approval of adefovir--we clearly have seen a new standard established regarding an NDA proposed for hepatitis B that I think really should become the standard regarding the global population, the experience of antigen positive, antigen negative patients, treatment experience patients and patients with co-morbid conditions.

DR. ENGLUND: Any final comments from the agency?

DR. BIRNKRANT: After you sum up I will make a brief comment.

DR. ENGLUND: Well, Dr. Wood took the

words from me. I was involved, and many of us here were involved in the meeting several years ago and I would just like to, for the whole committee, compliment and congratulate both the company and the agency for presenting us with a very complete, well-balanced and very well-documented and referenced study. I think it made our jobs much easier and we appreciate that.

I think we have been able as a committee to determine that entecavir is a new drug with a very favorable benefit, with potential risks that will be looked for and ascertained as studies go on, and we feel confident that that will be done with the overseeing of the FDA. We are happy with the trials, as Dr. Wood pointed out. It is wonderful to see big enough trials in the risk groups that we have been interested in, both the antigen positive and antigen negative and now, of course, the lamivudine resistant. So, that has

been very good to see and the data appears to us robust and when reanalyzed very well put together.

I think we still have some questions, as we do with any new drug, and these questions are important and we would expect some answers from the company. We hope to see these. We want to know the optimal duration of therapy. We aren't pinning you down on that yet because we understand trials are in progress but for clinicians this is critically important. We need to be able to tell our patients when they walk in the office that you are going to be on this drug for years or not.

We need to be able to get this into pediatrics. We have discussed this. We need to know what kind of follow-up we are going to need to do in our patients; who respond or don't respond to this therapy. And, we need to be able to give them advice about malignancy and the potential risk thereof.

I look forward, and we look forward as a committee, to hearing more about this in the future. So, thank you from the committee and I

will turn it over to Dr. Birnkrant.

DR. BIRNKRANT: Thank you. I would also like to thank the committee and the consultants for the lively and important discussions that were held today. They were quite helpful to us and we will take what was discussed today back to the agency so that we can continue our work on this application and work with Bristol-Myers Squibb in developing a strong and robust post-marketing plan as well. Thank you very much for all of your help.

DR. ENGLUND: Thank you. The meeting is adjourned.

[Whereupon, at 3:17 p.m., the proceedings were adjourned.]

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