sgg

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

VOLUME I

Monday, November 1, 1999

8:30 a.m.

Gaithersburg Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Scott M. Hammer, M.D., Acting Chairman
Rhonda W. Stover, R.Ph., Executive Secretary

Committee Members:

Henry Masur, M.D.
James J. Lipsky, M.D.
Roger J. Pomerantz, M.D.
John D. Hamilton, M.D.
Brian Wong, M.D.

Consultants:

Joseph S. Bertino, Jr., Pharm. D., Consumer Representative
Wafaa El-Sadr, M.D., M.P.H.
Judith Feinberg, M.D.
Jeffrey B. Kopp, M.D.
Women. Christopher Mathews, M.D., M.S.P.H.
Sharilyn K. Stanely, M.D.
Joel I. Verter, Ph.D.
Ram Yogev, M.D.

Guests:

Paul Kimmel, M.D.
Jeffrey Schouten

FDA:

Douglas Throckmorton, M.D.
K. Struble, Pharm. D.
Jeff Murray, M.D.
Heidi Jolson, M.D., M.P.H.
Sandra Kweder, M.D.
Greg Soon, Ph.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Introductions

DR. HAMMER: I think I would like to begin by having the members of the committee and the agency introduce themselves. Dr. Bertino, would you identify yourself for the transcriptionist and the audience, please?

DR. BERTINO: Joseph Bertino, from the Clinical Pharmacology Research Center Basset Health Care, in Cooperstown, New York, and I am serving today as the consumer rep.

DR. EL-SADR: I am Wafaa El-Sadr, Harlem Hospital in New York.

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

DR. FEINBERG: Judith Feinberg, University of Cincinnati, Infectious Diseases.

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

DR. YOGEV: Ram Yogev, Children's Memorial Hospital, Chicago.

DR. HAMILTON: John Hamilton, Duke University.

DR. MASUR: Henry Masur Clinical Center at NIH.

DR. LIPSKY: Jim Lipsky, Clinical Pharmacology, Mayo Clinic, Rochester, Minnesota.

DR. HAMMER: Scott Hammer, Infectious Diseases,

Columbia University.

MS. STOVER: Rhonda Stover, FDA.

DR. POMERANTZ: Roger Pomerantz, Infectious Diseases, Thomas Jefferson University in Philadelphia.

DR. VERTER: Joel Verter, George Washington University, guest statistician.

DR. KOPP: Jeffrey Kopp, Nephrology, NIDDK.

DR. KIMMEL: Paul Kimmel, nephrologist, George Washington University, leave of absence NIDDK.

MR. SCHOUTEN: Jeff Schouten, ad hoc community representative from Seattle, Washington.

DR. THROCKMORTON: Douglas Throckmorton, nephrologist in the Cardiorenal Division, Food and Drug Administration.

DR. STRUBLE: Kim Struble, FDA.

DR. MURRAY: Jeff Murray, FDA.

DR. JOLSON: Heidi Jolson, FDA.

DR. KWEDER: Sandra Kweder, FDA.

DR. HAMMER: Thank you very much. I would like to turn it over now to Ms. Stover, who will read the conflict of interest statement.

Conflict of Interest

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the

Columbia University:

MS. STOVER: Rhonda Stover, FDA.

DR. POMERANTZ: Roger Pomerantz, Infectious Diseases, Thomas Jefferson University in Philadelphia.

DR. VERTER: Joel Verter, George Washington University, guest statistician.

DR. KOPP: Jeffrey Kopp, Nephrology, NIDDK.

DR. KIMMEL: Paul Kimmel, nephrologist, George Washington University, leave of absence NIDDK.

MR. SCHOUTEN: Jeff Schouten, ad hoc community representative from Seattle, Washington.

DR. THROCKMORTON: Douglas Throckmorton, nephrologist in the Cardiorenal Division, Food and Drug Administration.

DR. STRUBLE: Kim Struble, FDA.

DR. MURRAY: Jeff Murray, FDA.

DR. JOLSON: Heidi Jolson, FDA.

DR. KWEDER: Sandra Kweder, FDA.

DR. HAMMER: Thank you very much. I would like to turn it over now to Ms. Stover, who will read the conflict of interest statement.

Conflict of Interest

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made part of the record to preclude even the

appearance of such at this meeting. Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting, with the following exceptions: In accordance with in accordance with 18 United States Code 208 full waivers have been granted to Drs. Mathews, Hammer and Masur. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr. El-Sadr's employer, the Harlem Hospital, was previously involved in an NIAID study of adefovir dipivoxil. Dr. El-Sadr had no involvement whatsoever in this trial...[house audio system problems]... because these studies are not primary studies to be discussed, the agency has determined, notwithstanding these involvements, that the interest of the government and the Dr. Hammer's participation outweighs the concern that the integrity...[house audio system problems] . ..therefore. Dr. Hammer may participate... [house audio system problems]... In the event that discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude

themselves from such involvement, and their exclusion will be noted for the record.

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

DR. HAMMER: Thank you. I would like to turn now to Dr. Jolson who will make some introductory comments.

Introductory Comments

DR. JOLSON: Good morning. I would like to welcome everyone to today's meeting in which we will discuss the application for accelerated approval of adefovir dipivoxil for the treatment of HIV.

First, I would like to extend a special welcome to our invited consultants who are joining the committee today. I would also like to welcome Gilead Sciences, the sponsor of today's application.

The efforts of Gilead in developing this product should be commended for three specific aspects of their overall drug development. Specifically, I would like to acknowledge their efforts in conducting investigations for treatment experienced patients; their ongoing commitment to providing an avenue for expanded access; and their development of a sizeable database on viral resistance.

[Slide]

The database supporting today's application is complex in several respects. Before we hear the actual data presentations, I thought it might be useful to provide some of the regulatory framework and other points to consider as a backdrop for today's deliberation.

Because it has been about a year since this committee has considered an application for accelerated approval, which was the abacavir NDA, I would like to start today's meeting with a very quick review of FDA's provisions for accelerated approval. Next, I will explain how the Division of Antiviral Drug Products actually implements this regulation with regard to what we expect to see in submissions for accelerated and later traditional approval of antiretrovirals, and the advice we will provide on trial design. As you will hear more about today, the development of adefovir raised several challenges, and I will discuss how the general requirements for accelerated approval have been tailored to the circumstance of this application.

As the committee is aware, the sponsor elected to pursue marketing a dose that is lower than that studied in most of the Phase III development because of dose-limiting nephrotoxicity. Therefore, I will briefly discuss our guidance to sponsors in similar circumstances, that is, whenever a product change is made that significantly impacts the pharmacokinetic profile of an already studied drug.

Last, I will end with some general points to consider on equivalence trial design and labeled indications that I would like the committee to bear in mind as they consider today's application.

[Slide]

Most of you are already aware that the accelerated approval regulations were enacted to allow patients with serious and life-threatening illness access to approved, safe and effective therapies where the approval would be based on endpoints that would occur at a time point earlier in trials than the ultimate disease outcome of irreversible morbidity or mortality. Hivid or ddC was the first product for HIV to be approved under this regulation, and Agenerase or amprenavir was the most recent.

This provision is intended to be applied to those therapies that provide a meaningful therapeutic benefit to existing treatment, and the regulations provide examples such as demonstration that a new product can treat patients unresponsive or intolerant to available therapies, or demonstration that a new product is associated with an improved response over available therapies.

The phrase "meaningful therapeutic benefit" is obviously highly subjective, and in practice we have accepted a variety of ways that a product may be considered as having a therapeutic advantage, including an improved

efficacy or safety profile, an improved dosing schedule, a novel mechanism of action, or a different clinical cross-resistance profile.

The key feature of this regulation is that it provides for initial or accelerated approval based on either surrogate endpoints which are laboratory based, such as HIV RNA and CD4 for HIV therapeutics, or clinical endpoints that would occur earlier in the disease process and before irreversible morbidity and mortality. At some time post-marketing a sponsor may then apply for traditional approval on the basis of additional data to verify the clinical benefit of the initial finding.

[Slide]

Given that the accelerated approval provisions are not limited to HIV, the division has needed to develop guidance for how these regulations are to be implemented in the ever-changing field of HIV therapeutics. The division's approach to accelerated approval has evolved considerably over the years reflecting changes in clinical management, the availability of potent therapies, and the availability of standard assays for the measurement of HIV RNA. Our current advice on this topic is available in a draft guidance document to industry. It is available on the web site noted on the slide, and reflects the consensus reached at the July, 1997 Surrogate Marker Advisory Committee

meeting that demonstration of sustained viral suppression is evidence of clinical benefit.

I will briefly comment on a few key features of our guidance. In general, for accelerated approval the division expects that a new drug application will contain the results of at least two adequate and well-controlled trials that provide safety, laboratory and clinical data on patients through at least 24 weeks of treatment in all patients.

Further, it is expected that the plans for traditional approval will be solidified and trials will be well under way prior to granting an accelerated approval.

Traditional approval may be subsequently considered on the basis of data reflecting treatment through at least 48 weeks. Often this longer-term data comes from the same studies that were submitted in the original NDA.

[Slide]

Our guidance also provides some general advice on trial design, and provides for flexibility, the choice of overall design as appropriate for the patient population, and the hypothesis to be tested.

In the spirit of accelerated approval, sponsors are specifically encouraged to investigate their product in the patient population most in need of new therapeutic options, specifically the heavily pretreated patient

population. Because we support the use of more than one investigational product in a protocol and recognize its need, particularly for treatment experienced patients, our guidance includes the reminder that registrational studies need to be designed to demonstrate the contribution of each investigational component of regulatory interest.

Last, in the era of multi-drug regimens for HIV and other concomitant medications, we stress the need to evaluate the potential for drug-drug interactions prior to launching large clinical studies. This recommendation is based on the concern that unexpected drug interactions may both adversely impact patient safety and product efficacy.

[Slide]

There are two important caveats regarding the accelerated approval regulation and our guidance on its implementation. First, as mentioned, this regulation allows approval based on endpoints that can be measured at earlier time points in clinical trials, and this is the major feature that provides for earlier access to approved therapy. However, accelerated approval does not change the standard of evidence for efficacy required by the Food, Drug and Cosmetic Act as amended in 1962. This amendment stipulates the requirement for substantial evidence, which is defined as evidence from adequate and well-controlled investigations that allow the conclusion that the drug will

have the effect that it claims.

The second caveat is that our guidance outlines a minimum set of clinical requirements for an accelerated approval application. There will be, inevitably, circumstances where longer duration or additional data are necessary to evaluate unique safety or efficacy issues prior to approval.

[Slide]

As you will hear in the presentations today, two additional expectations for the submission of an accelerated approval NDA for adefovir were discussed with the sponsor. Both of these requirements were necessitated by the identification of dose-limiting nephrotoxicity with adefovir during the conduct of the principal Phase III trials.

First, based on the discussion with the advisory committee members, the division recommended that at least 48 weeks of data at the proposed marketing dose be provided with the initial NDA submission. This length of follow-up was recommended because available data at the time suggested that nephrotoxicity did not become readily apparent until at least 20-24 weeks of dosing.

Second, the sponsor was made aware that because substantial clinical development of the 120 mg dose had already occurred, comparability between the 120 mg dose and the 60 mg proposed for marketing dose would need to be

conclusively established.

[Slide]

There are a variety of circumstances when there is a substantial change in the pharmacokinetic profile of an already studied drug, either pre- or post-approval. Although today's application provides for a change in dose due to toxicity considerations, other examples include changing the frequency of administration for convenience, such as changes from TID to BID regimens or BID to QD regimens, and changes in formulations, such as enteric coating.

[Slide]

The recommendations on this slide would apply to any of these circumstances. So, in any of these circumstances that were just outlined, sponsors are required to establish the comparability between the old and the new product regimen by providing either data that the pharmacokinetic difference isn't clinically relevant or clinical trial data to demonstrate comparability of clinical benefit with the new product.

[Slide]

For approved, well-established products we are often asked why there need be a requirement for new clinical trial data. In general, when changes significantly impact on the pharmacokinetic profile we require clinical data to

provide assurance that the new product, dose or regimen is safe and effective and not inferior to the already proven product. For antivirals, shorter-term data of several weeks is inadequate to demonstrate comparable efficacy because differential resistance may not become apparent until later in treatment. Similarly, it is extremely difficult to establish compelling pharmacokinetic-pharmacodynamic relationships based on shorter-term clinical data.

In practice, we have routinely advised sponsors that the division will accept and review trial data reflecting 24 weeks of treatment, with a Phase IV commitment to provide at least 48 weeks of follow-up.

[Slide]

The trial that is submitted to establish the comparability of the proposed dose for marketing with the originally studied adefovir dose, and that is trial 417, is a critical component of the overall adefovir application. Trial 417 is an active control, equivalence design trial, and I would like to provide some points for the committee to consider when interpreting trials with this design.

The agency as a whole has had a great deal of experience analyzing results from equivalence trials across a broad range of therapeutic indications, and this division has had some experience with equivalence trials for both non-HIV and HIV indications in selected settings. However,

we have had very limited opportunity to consider an equivalence trial as the basis of approval of an antiretroviral in the complex setting of combination drug therapy and treatment experienced individuals, and we will look forward to the committee's discussion of this issue as it relates to today's application.

The three slides that follow cover some general points to consider about interpretation of equivalence design trials. My reference for these comments is available on the CDER web page in the form of a draft guidance that was developed by the ICH, the International Conference on Harmonization, on the choice of control groups in clinical trials.

[Slide]

The intent of an active control equivalence trial is to show the efficacy of the test drug by showing that it is as good as, equivalent and not inferior to a known effective agent. This design raises an inherent critical question of whether the trial is capable of distinguishing active from inactive treatment. The capability of a study to do just this rests on the critical assumption that the active control drug, in this case for today's application it is the 120 mg dose of adefovir, will have had an effect of a defined size in the study. In the absence of a placebo comparator, the efficacy of the active control relies on

implicit historical experience such that trials of the active control, when adequately powered, regularly distinguish active drug from placebo in a similar patient population and under similar conditions of use.

[Slide]

A second point to consider relates to the so-called non-inferiority margin. Prior to initiating the trial an equivalence or non-inferiority margin is established, also called the delta. This margin is the degree of inferiority of the test drug compared to the control that the trial will attempt to exclude statistically. However, there in general are no agreed upon statistical conventions for an acceptable margin of inferiority. These are matters of clinical judgment and are determined on a case by case basis. In general, the margin chosen for a trial cannot be greater than the smallest effect size that the active trial would be reliably expected to have compared with placebo in a setting of the planned trial. Even smaller margins based on clinical judgment may be desired.

Our draft guidance suggests that a delta of 10 percent may be used for sample size calculations, with the caveat that smaller or larger deltas may be acceptable depending on the expected effect size of the active control. These considerations raise questions about how acceptable

Non-inferiority margins should be determined for antiretrovirals used in combinations, especially when the product of interest is unlikely to be the more potent component of a particular combination regimen.

[Slide]

The last point to consider on the interpretation of equivalence design trials is a reminder to take into account the particular study circumstances that may make treatment arms look more similar in a trial of this design. A few of the factors that may reduce the trial's ability to detect true differences include poor compliance, or discontinuation of therapy, substantial loss to follow-up, overall poor responsiveness of the study populations to treatment effects, and use of concomitant medications that may interfere with the ability to assess the contribution of the test drug.

[Slide]

I will close my remarks with a comment relating to the sponsor's proposed indication and the division's policy for labeled indications for antiretroviral drugs. The labeled indications for antiretrovirals, as everyone knows, have evolved considerably over the past decade, reflecting both the availability of more products and recommendations for their use in combination. Currently, unless a product has a significant safety or efficacy limitation it would

receive the indication on the slide.

Other indications can always be considered, and for today's application the sponsor has requested a more limited interaction for patients with prior nucleoside analog treatment experience based on safety considerations. However, because the labeled indication does not limit how a product is used in clinical practice, we will ask the committee today to consider risks and benefits both for the proposed indicated population and for the broader population of HIV-infected individuals in whom the product might be used in clinical practice.

Thank you for your attention, and we will look forward to discussion and deliberation on the questions that this application poses. Dr. Hammer, I will turn the meeting back to you.

DR. HAMMER: Thank you very much, Dr. Jolson, for putting the framework together for our meeting today. I would like to turn now to the sponsor presentation from Gilead Sciences and Dr. Jaffe, I believe, will open the presentation.

Sponsor Presentation

Overview of Development Program

DR. JAFFE: Good morning.

[Slide]

My name is Howard Jaffe, from Gilead Sciences, and

today we are here to review our new drug application for adefovir dipivoxil for the treatment of HIV-infected patients.

Joining me from Gilead are Jay Toole, who will review the results of our clinical trial and Norbert Bischofberger, who will review our HIV resistance studies. Additionally, we have various consultants who have participated in the adefovir development program who are here to provide their insights as well. We ask that you hold your questions until the end of our presentation.

When we began testing adefovir in 1994 the only available HIV therapies were nucleoside RT inhibitors. Since then the landscape of HIV therapy has changed dramatically, as have the number of treatment options.

[Slide]

Captured on this slide are the percent of HIV created patients according to ART regimens received and the mean length of time on each regimen. As you can see, 41 percent of patients are currently receiving their first ART regimen for an average of about 11 months; 23 percent of patients are on their second regimen for an average of about 8 months. The last grouping, those patients representing about one-third of the patients receiving HIV therapy, received their therapies on average 5-8 months.

The complex and interrelated issues of viral

resistance inherent difficulties and drug toxicity lead to a successionally declining course with each new treatment regimen. Patients in the second and third groups have an urgent need for new treatment options, and these are the patients for whom adefovir dipivoxil is intended.

[Slide]

Adefovir dipivoxil is the pro-drug of adefovir, the first of a new class of nucleotide analog for reverse transcriptase inhibitors. It has a unique resistance profile with activity in HIV resistant to 3TC, as well as virus with combined AZT and 3TC resistance. This is important because over 90 percent of patients will pass through AZT and 3TC treatment during their course of therapy.

Additionally, unlike other antiretrovirals, the use of adefovir is unlikely to lead to the development of resistance and, therefore, the likelihood of limiting future treatment options is low.

Adefovir also has once daily dosing, without dietary restriction, and this is particularly attractive for simplifying dosing regimens and for particular clinical settings, such as those requiring directly observed therapy.

The most important risk of adefovir is dose-limiting nephrotoxicity. However, through extensive clinical testing of 120 mg once per day, twice the dose

sought for approval, the risk of nephrotoxicity has been well characterized. It can be monitored with monthly routine lab tests and, importantly, when it does occur it is largely reversible with drug discontinuation.

[Slide]

To understand the potential benefits of adefovir, we need to start with its virology. In vitro adefovir selects for the J65R and K70E RT mutations. The K65R has been seen in association with ddI and ddC use. The K70E mutation is a novel mutation. Both mutations have been observed only rarely. Most importantly, adefovir maintains activity against HIV resistant to nucleoside RT inhibitors.

Dr. Bischofberger will review the clinical virology in more depth later on in our presentation. However, we should take note that adefovir has increased activity against 3TC resistant virus, the M184V mutation, and while it has less activity against high-level AZT resistant virus, the combination of high-level AZT resistance and 3TC resistance renders the virus near wild type in terms of susceptibility to adefovir. This compliant resistance genotype, high-level AZT and 3TC, is a highly prevalent genotype in treatment experienced patients.

[Slide]

Looking at the risks of adefovir, nephrotoxicity is the major dose-limiting toxicity. It has a consistent

pattern of onset and can be readily monitored. Together, serum creatinine and phosphate are highly sensitive and specific for detecting adefovir-related nephrotoxicity. Consistent with a predominantly proximal tubular effect, decreased bicarbonate, non-nephrotic range proteinuria and glycosuria may also be observed. Changes in creatinine and phosphate form the basis for management guidelines for drug discontinuation, with mild changes in creatinine, that is 0.5 mg/dL increases above baseline or decreases in serum phosphate to less than 1.5 mg/dL, leading to drug discontinuation. Clinical trial results demonstrate that adherence to monthly monitoring and management guidelines are necessary to reduce the risk of clinically significant toxicity.

[Slide]

In considering our data package, it is necessary to review various program milestones. Clinical testing began in 1994 and included short-term dosing, monotherapy versus placebo studies for up to 12 weeks of doses ranging from 125 to 500 mg once per day, with the demonstration of good tolerance, significant anti-HIV activity and the unique resistance profile.

We met with FDA in 1996 to discuss a program for potential licensure. At that time, one pivotal study, study 408, was discussed in which patients failing background

antiretroviral therapy would have 120 mg of adefovir or placebo randomized to their therapy.

The program continued to move forward and, in December of 1997, we initiated an expanded access program at the 120 mg dose for patients who previously failed nucleoside RTIs and protease inhibitor therapy. However, shortly afterwards, with the unblinding of study 408, the extent of adefovir-related nephrotoxicity became evident. Given the therapeutic index for the 120 mg dose, we and the FDA sought the guidance and advice of the Antiviral Advisory Committee last year in a closed meeting. At that meeting, we discussed the target interaction; we discussed the size and duration of the safety database, in which we adequately characterized the risk and reversibility of nephrotoxicity; and we discussed dosing regimens, including looking at doses at 60 mg once per day. With the successful completion of studies involving 60 mg, we filed our NDA in June of this year.

[Slide]

Today, we return to review these new results which include over 5000 adefovir-treated patients with up to 3 years of follow-up. The risk and reversibility of adefovir-related nephrotoxicity has been well characterized. The mechanism of toxicity is better understood, and management guidelines have been refined and broadly tested in an

expanded access program. We have chosen the 60 mg once per day dose on the basis of results from monotherapy and combination therapy studies.

[Slide]

Based on the risks and benefits associated with adefovir, we are seeking a second-line indication for use in combination with other antiretrovirals for the treatment of patients with clinical immunologic or virologic progression despite prior RT inhibitor use.

Dr. Toole will now review the clinical trial results.

Clinical Trial Results

[Slide]

DR. TOOLE: This morning Gilead Sciences will present clinical trial results for 120 and 60 mg dose levels of adefovir dipivoxil. Although seeking approval at the 60 mg dose level, we were well into our Phase II/III studies at the 120 mg dose before recognizing that nephrotoxicity was the most important dose-limiting toxicity. This led us to investigate the 60 mg dose for activity and an improved safety profile.

Our NDA was submitted for both of these doses in over 5400 patients including over 500 females, over 1600 African American and Hispanic patients, as well as 38 children. These patients were administered adefovir once

daily on the basis of a long intracellular half-life of up to 30 hours for the active moiety.

Adefovir dipivoxil is an oral pro-drug with good bioavailability in a fasted or fed state. Following absorption of the pro-drug, adefovir is eliminated by urinary excretion with equal contributions from both filtration and secretion. Adefovir is not a substrate inhibitor nor inducer of the cytochrome p450 enzyme system.

Based on several studies, there is no evidence for drug-drug interactions from the nucleoside class AZT, 3TC or abacavir; from the non-nucleoside class delavirdine or efavirenz; from the protease inhibitor class indinavir, nelfinavir and saquinavir. There has been a slight increase in ddI exposure observed at the 60 mg dose, however, there is no increase in ddI-related adverse events in patients that received the 120 mg dose of adefovir and ddI.

Earlier this year at the retrovirology conference, pharmacokinetic data were presented from ACTG 359 which indicated an interaction with adefovir, delavirdine and saquinavir. However, as just stated, these observations are not consistent with our data. Additional pharmacokinetic results are pending from the ACTG 398 which will also include saquinavir.

[Slide]

For the clinical trial overview I will briefly

discuss our Phase I/II dosing experience which provides information on our short-term dosing. Then I will discuss in more detail study 408, which was our registrational study and which is important because it has extensive follow-up /which has allowed us to characterize the resolution of nephrotoxicity. In addition, I will discuss CPCRA 039, which is important because it provides long-term placebo control data whereas, in study 408 patients received placebo for 24 weeks before receiving adefovir dipivoxil in the open-label phase. Study 411 provides important controlled efficacy information in treatment naive patients.

[Slide]

We conducted two Phase I/II studies, studies 402 and 403, which examined once daily dosing from 125-500 mg for 2-12 weeks duration. In these studies we observed dose-dependent, reversible side effects, primarily gastrointestinal symptoms as well as asymptomatic transaminase elevations. We also observed asymptomatic decreases in serum carnitine, and this has led us to provide supplementation for our Phase II/III studies.

We observed anti-HIV activity which was similar whether patients were treatment naive or treatment experienced. We also saw a similar reduction in HIV viral load across the dose groups.

[Slide]

An example of this can be seen in study 403, which was a randomized, placebo-controlled study with a 6-week double-blind phase followed by a 6-week open-label phase. Shown here are the mean changes from baseline with 95 percent confidence intervals, showing that for both doses there is about a 0.4 log decrease in baseline, and at all time points they are statistical significantly different from placebo based on a non-overlap of the 95 percent confidence intervals.

The activity observed is maintained out through week 12 and, importantly, patients who received placebo who go on to receive adefovir in the open-label phase also show a 0.4 log decrease. Based on better tolerability of the lower dose, we chose a 120 mg dose for our Phase III study, study 408.

[Slide]

In this study, patients were randomized to receive either adefovir or placebo entered onto a background regimen in heavily pretreated patients, and these patients had a median duration of prior treatment of over 3.5 years.

The study was conducted with a 24-week double-blind period followed by an open-label phase. The entry criteria were that patients had to be on a stable regimen for at least 8 weeks, and HIV RNA greater than 2500 and CD4 counts greater than 200. The primary efficacy endpoints

were average change, denoted as DAVG24, in both HIV RNA and CD4 cell counts.

[Slide]

There were 442 patients randomized to the study, and the arms were well matched at baseline, with a mean HIV RNA of about 30,000, mean CD4 cell count of about 350, and the patients were also well matched for their background regimen. Adefovir was well tolerated over 24 weeks, as indicated by 18 percent and 14 percent from the active and placebo groups discontinuing: 13 percent of patients discontinued adefovir for an adverse event, and the majority of these were due to gastrointestinal symptoms or transaminase elevations.

The activity we observed was consistent with that seen in study 403, as shown by the mean change from baseline of the two treatment arms. Again, we see about a 0.4 log change from baseline at week 24, and at all time points during the study this activity was significantly different from placebo as shown by the non-overlap of the 95 percent confidence intervals. At week 24 the difference is significant with a p-value less than 0.001. The activity seen at week 24 is maintained out through week 48. Patients who received placebo and then went on to receive adefovir in the open-label phase also show a 0.4 log decrease after 24 weeks. Importantly, this difference between the placebo

group and the active group is consistently observed independent of age, gender, race, HIV RNA or CD4 cell strata, or is independent of whether the patients were receiving a protease inhibitor at baseline or not.

[Slide]

The DAVG24 was also significant, as shown here looking now at the mean DAVG24 using the bDNA assay, which is the particle specified assay. There was a minus 0.24 log change compared to little change for placebo. Prior to unblinding these samples were also assayed using the PCR technique and, as shown, these results were confirmatory.

[Slide]

DAVG24 for CD4 was not significant, as shown here. But looking at the changes for week 24 for mean and median both favored the active group, and these were significantly different.

[Slide]

During the first 24 weeks we observed few grade 3 or 4 clinical adverse events, as shown here, and these were limited to headache and diarrhea.

[Slide]

There were more grade 3 or 4 laboratory abnormalities, and the most common was elevation in creatinine kinase. However, this occurred more commonly in the placebo group compared to the active group. ALT and AST

transaminase elevations, as well as hyperbilirubinemia, were observed more commonly in the active arm.

[Slide]

To expand our view to look at all patients who received adefovir as well beyond 24 weeks, there was a total of 403 patients, including 187 patients that were initially randomized to receive placebo. This group had a median duration of treatment of 9 months, extending out to 2.5 years, and a median duration of follow-up of 20 months, extending out over 3 years.

[Slide]

The grade 3 or 4 clinical abnormalities observed in the overall study again showed gastrointestinal symptoms but now we see the emergence of nephrotoxicity, reported as a Fanconi-like syndrome, in 1 percent of the patients.

[Slide]

The laboratory abnormalities associated with nephrotoxicity were more common. These were defined as a creatinine increase of 0.5 mg/dL or greater, hypophosphatemia, decreased serum bicarbonate, proteinuria and glycosuria. For these parameters, these correspond to grade 2 or higher laboratory abnormalities. These were defined on the basis of variability observed in the placebo group during the first 24 weeks of the study.

[Slide]

Shown here is the Kaplan-Meier analysis looking at the time to onset for serum creatinine increase of 0.5 mg/dL or greater looking at the percentage of patients out through week 80, and shows that prior to week 20 there were very few events, after which the event rate increases reach an apparent plateau with about a 50 percent incidence at week 80.

Looking at a serum creatinine of 2 mg/dL or greater, an absolute value, again shows very few events prior to week 28, then out through week 80 about 5 percent of the patients are affected. This demonstrates that these abnormalities are common in adefovir-treated patients.

[Slide]

Looking at the severity of these abnormalities based on the data supplied to the central laboratory, grade 2 abnormalities were observed in about 5 percent of the patients.

[Slide]

The delayed onset for nephrotoxicity was also observed with hypophosphatemia, with a similar time to onset as that observed for serum creatinine increase. The severity, as shown by the grade of toxicity, indicates that 42 percent of the patients developed hypophosphatemia less than 2.0, with 2 percent of the patients developing a grade 4 abnormality.

[Slide]

Many of these patients developed both of these abnormalities concomitantly, and that is shown in the following Venn diagram. Of 168 patients that developed a serum creatinine increased, represented here, 117 had concomitant hypophosphatemia. Similarly, for the 166 patients that developed hypophosphatemia, as shown here, 49 developed that in isolation.

[Slide]

These patients with nephrotoxicity were followed for resolution, and the criteria were that resolution must be sustained through last follow-up. For increased creatinine, decreased bicarbonate or phosphate, the definition was that it had to be sustained within 2 standard deviations of the mean change from baseline observed in the placebo group during the first 24 weeks of the study.

For proteinuria it had to be sustained less than or equal to 1+, and for glycosuria less than or equal to trace.

[Slide]

Two standard deviations for serum creatinine is 0.4 mg/dL. Shown here is the Kaplan-Meier looking at the resolution to that level for the 168 patients who had a 0.5 mg/dL increase from baseline. Looking at the percentage of patients out through week 100, this demonstrates that the

median time to resolution was approximately 17 weeks, and that with extended follow-up greater than 95 percent of the patients will have resolved.

[Slide]

Resolution for the other laboratory parameters are summarized here, showing that resolution has a median time of 16 weeks for proteinuria and, as I just showed you for creatinine, 17 weeks. Importantly, for each of these parameters the Kaplan-Meier's indicate that greater than 95 percent of the patients will resolve.

[Slide]

These observations are based on a Kaplan-Meier analysis. The observed data are shown here and indicate that from 10 percent to 19 percent of the patients that developed the abnormality did not resolve at last follow-up. However, looking at this group of patients that remain unresolved, with regard to median follow-up time, it indicates that, as shown in this column, their duration of follow-up is limited when comparing those patients to the patients that have resolved which have a median time of follow-up of 50 weeks.

[Slide]

The conclusions drawn from study 408 are that we observe a durable reduction in HIV RNA in RTI-experienced patients. That reduction was a 0.4 log decrease and it was

independent of age, gender or race.

Activity was also observed in patients that received adefovir in the open-label phase, and this activity observed after 24 weeks was maintained out to 48 weeks of closing. Adefovir dipivoxil is well tolerated through 24 weeks, during which we primarily observed gastrointestinal side effects. After 24 weeks dose-limiting nephrotoxicity was observed, and this demonstrates the value of monthly laboratory monitoring.

In addition, and importantly, through Kaplan-Meier analysis, greater than 95 percent of the patients are estimated to resolve.

[Slide]

The 120 mg dose of adefovir dipivoxil was also utilized in study CPCRA 039. This study was sponsored by the NIH and conducted by the Community Program for Clinical Research on AIDS, a network of over 100 community based clinical practices.

In this study patients were randomized to receive either adefovir or placebo added onto background therapy. The primary endpoint was survival. Additional secondary clinical efficacy endpoints included progression of disease as well as development of opportunistic infections. The original sample size was 2200 patients.

In August of 1998, following a recommendation by

the DSMB, the study was discontinued, and that was in recognition of the decline in the event rate following the introduction of protease inhibitors, which would have required the study to enroll over 4000 patients to be adequately powered. At that time, just over 500 patients were enrolled and it was deemed impractical to continue. The study was not discontinued for safety reasons and, in general, the safety profile observed was consistent with that observed in study 408.

Because of the long-term placebo control, this study provides important safety data, and also allows us to characterize the background of renal-related laboratory abnormalities.

[Slide]

The data here provide a safety overview for study 039 and show that by 12 months the discontinuation rate is similar between the active group and the placebo group, with 38 percent of the patients discontinuing adefovir compared to 32 percent on the placebo arm. An identical percentage of patients developed either a grade 4 adverse event or a toxicity which required discontinuation. With the exception of nephrotoxicity, these abnormalities are equally distributed in the two treatment groups. There were more patients on placebo, 31 percent compared to 25 percent, that had grade 4 adverse events. There were 17 deaths on the

active arm, 16 deaths in the control arm, and 1 death in each treatment group had renal failure as an investigator-assessed contributor to mortality.

[Slide]

The laboratory abnormalities associated with nephrotoxicity are shown here, and indicate for the placebo group that 2+ proteinuria was observed in 21 percent of the patients. Six percent of the patients developed a serum creatinine increase of 0.5 or greater, and 8 percent of the patients developed hypophosphatemia to less than 2 mg/dL.

Comparing the active group to the placebo arm for changes in creatinine and phosphate indicate that these changes are more sensitive markers than glycosuria, and more specific markers than decreased bicarbonate or proteinuria.

Also, looking at the changes in serum creatinine and hypophosphatemia shows that the 27 percent and 24 percent is notably less than that observed in study 408 where this event rate was 40 percent for each of these markers. This may reflect the fact that there was increased investigator awareness in study 039, as well as the implementation of monthly monitoring which was required in study 039 whereas in study 408 monthly monitoring was done through week 24, after which it was done on an every 2-month basis, at which time patients were at greatest risk for development of nephrotoxicity.

[Slide]

While the safety conclusions from study 039 are generally consistent, the effect on viral load was not. There was no difference between adefovir and placebo at either 6 or 12 months. However, the study was not optimally designed to look for virologic efficacy. That is, unlike study 408, changes in background retroviral therapy were permitted any time prior to, at, or following randomization. Therefore, a stable baseline viral load was not established. In addition, there was no viral load entry criterion or stratification based on that criterion.

This led to an imbalance in baseline viral load where the placebo group had a 3-fold higher viral load compared to the active arm. Possibly due to this increased viral load in the placebo arm, there was a significant increase in the addition of antiretroviral therapy by month 2 compared to the active arm.

[Slide]

Studies 408 and 039 were conducted in treatment experienced patients. We also looked at adefovir activity in treatment naive patients in study 411. This is a randomized study of adefovir and indinavir in combination with either AZT, 3TC or D4T, and there was a control arm of AZT, 3TC and indinavir. Patients were antiretroviral naive, with CD4 counts greater than 100, and HIV RNA greater than

5000. The baseline characteristics showed a mean HIV RNA log of 4.6 and a mean baseline count of around 400.

[Slide]

There were 224 patients randomized into one of five treatment groups, either the control arm, one-third adefovir-containing 3-drug regimens, or a quadruple drug regimen. The primary endpoint was the proportion of patients that had less than 400 copies/ml at week 20. Secondary endpoints included changes in HIV RNA.

[Slide]

Starting with the primary endpoint, this graph looks at the percentage of patients from baseline to week 20 that have less than 400 copies/ml using an intent-to-treat analysis. As shown, both the control group as well as the adefovir plus 3TC arm have similar activity.

[Slide]

A summary of the week 20 efficacy data for the control group as well as the 3 adefovir-containing 3 drug regimens is shown here looking at HIV RNA less than 400 with an intent-to-treat analysis or looking at the mean change in HIV RNA at week 20.

Looking at these percentages, the data indicate that the adefovir-containing 3 drug arms have similar activity compared to the control arm with respect to HIV RNA Less than 400. In addition, similar activity is observed

when looking at the mean change from baseline at week 20. Also, comparing the data from patients that were receiving adefovir plus 3TC plus indinavir to the control column indicates that adefovir can substitute for AZT with resulting similar efficacy.

Comparing the data in this column, where patients received adefovir and AZT and indinavir, indicates that adefovir can substitute for 3TC, again, with resulting similar efficacy.

[Slide]

The quadruple drug regimen data provided no additional efficacy beyond the 3-drug regimens. Substitution of adefovir for either AZT or 3TC resulted in similar efficacy when looking at the proportion of patients that had less than 400 copies/ml or HIV RNA changes from baseline to week 20.

The incidence of nephrotoxicity and the lack of a dose response observed at the 125 mg and 250 mg doses led us to examine a 60 mg dose for activity and an improved safety profile.

[Slide]

For the clinical trial overview of 60 mg, I will discuss study 420, which was our monotherapy study; study 417, which directly compares the 60 mg and 120 mg dose levels; and I will also discuss our experience from expanded

access for the first 1000 patients that received adefovir at the 60 mg dose level.

[Slide]

Study 420 was a randomized, double-blind, placebo-controlled study with patients randomized 2:1 active to placebo in therapy-naive patients. The study was for 4 weeks, and the entry criteria were HIV RNA greater than 5000 and CD4 cell counts greater than 150. The because characteristics for the 2 treatment arms were well matched, and the primary efficacy endpoint was average change, denoted as DAVG4, over the 4 weeks of dosing.

[Slide]

The efficacy results we observed were consistent with our earlier studies, as shown by looking at the mean change from baseline out through week 4 comparing the 2 treatment arms.

For the 60 mg dose we observed about a 0.3 log decrease from baseline, which at each time point is significantly different from placebo as demonstrated by the non-overlap of the 95 percent confidence intervals, and the corresponding p-values at each time point are shown below.

Consistent with the drug effect following completion of dosing at week 4, there is a return towards baseline in the active arm. The DAVG4 also shows significant activity.

[Slide]

Here, we are again looking at the mean DAVG4. 'here was a minus 0.3 log change in the active group, little :hange in the placebo group, and the result was highly ;ignificant.

[Slide]

The conclusions from this study are that adefovir nonotherapy at 60 mg provides significant anti-HIV activity :ompared to placebo. In addition, the effect is similar to :hat observed in earlier studies at the 125 mg and 250 mg doses in studies 402 and 403 which were for 2-6 weeks duration.

[Slide]

To establish equivalence of the 60 mg and 120 mg doses, we conducted study 417. This study was a randomized, double-blind study of adefovir at 2 dose levels in combination therapy. In this study patients had to be protease inhibitor naive and have at least 4 weeks of prior nucleoside experience, with HIV RNA greater than 5000 and CD4 cell counts greater than 100.

The objectives of the study were to determine the relative tolerability of the 2 doses, as well as to establish equivalence of the 2 doses with regard to anti-HIV activity.

[Slide]

There were 214 patients randomized, 109 to the low dose, 105 to the high dose. There was additional randomization to one of three treatment arms, either a dual protease where patients received nelfinavir and saquinavir, or nelfinavir plus one nucleoside reverse transcriptase inhibitor, or saquinavir plus one nucleoside reverse transcriptase inhibitor. The NRTI was chosen from among AZT, 3TC or D4T depending upon the patient's prior experience.

[Slide]

The baseline characteristics for the patients were well matched, with mean HIV RNA of about 40,000, mean CD4 cell counts of about 360.

[Slide]

The patient disposition out to week 20 indicates the 60 mg dose is better tolerated in the 120 mg dose. As shown here, 14 patients discontinued the low dose compared to 26 at the high dose. Three of these were due to adverse events at the low dose compared to 13 at the high dose. Again, we observe a dose relationship for gastrointestinal toxicity as 2 discontinued for that reason at the low dose compared to 9 at the high dose. One patient at the low dose and 2 patients at the high dose discontinued for transaminase elevation. Two patients in the higher dose group discontinued for reasons unrelated to adefovir.

[Slide]

The better tolerability at the lower dose is also shown by looking at the time to discontinuation from the overall study. Shown here is a Kaplan-Meier analysis looking at the percentage of patients out to week 48 that discontinued the study, indicating that at the higher dose the percentage is always greater than at the lower dose. This result is statistically significant. It is also important to note that many patients discontinued from both dose groups after week 24 due to insufficient viral load suppression.

[Slide]

The primary efficacy endpoint of the study was the proportion of patients with less than 400 copies/ml at week 20. Secondary endpoints included changes in HIV RNA from baseline out through week 20.

[Slide]

The 2 doses have similar activity, as shown by this graph which shows the percentage of patients from because out to week 20 with less than 400 copies/ml using an intent-to-treat analysis for the 60 mg dose and the 120 mg dose, with the 60 mg dose resulting in 41 percent of patients at week 20 less than 400 compared to 31 percent of the patients at the 120 mg dose.

[Slide]

The primary objective was to establish equivalence, and the criteria we employed was a 2-sided 95 percent confidence interval for the difference in the /primary efficacy endpoint. To demonstrate equivalence of the lower dose, the lower boundary of the 95 percent confidence interval could be no greater than minus 10 to minus 12 percent. Applying these criteria, we found that equivalence was established.

[Slide]

This summarizes the data for the equivalence analysis using 3 different methods. First, looking at the intent-to-treat analysis where missing observations are considered failure, as just shown in the previous graph, there were 41 percent of the patients at the low dose, 31 percent of patients at the high dose, an actual difference of 10.7 percent, and a lower bound of the 95 percent confidence interval of minus 1.7.

Looking at the as treated analysis, there were 48 percent of the patients at the low dose, 45 percent of the patients at the high dose, an actual difference of 3.3 percent, and now the lower bound of the 95 confidence interval with this analysis was minus 11.3.

Because the higher discontinuation rate observed at the higher dose could be biasing the intent-to-treat analysis, we also performed an analysis where the last

observation was carried forward to week 20. Using this method, there were 42 percent of patients at the low dose, 37 percent of the patients at the high dose, a difference of 5.4 percent, and now the 95 percent of the lower bound is minus 7.3.

So, for each of these methods the lower bound of the 95 percent confidence interval was less than minus 12 percent in magnitude.

[Slide]

The study was not powered to look for differences either between the arms or within the dose groups of each arm. However, a notable difference was observed when looking at the saquinavir plus NRTI arm, as shown here, in which 49 percent of the patients were less than 400 at the low dose compared to 20 percent at the high dose. However, it is important that this large disparity was not observed at week 12, with the corresponding percentages of 54 percent for the low dose and 40 percent for the high dose. In addition, the other saquinavir-containing arm does not show disparity, where 42 percent and 44 percent of patients at the low and high dose respectively were less than 400 using an intent-to-treat analysis.

[Slide]

The difference between doses in this treatment group is less striking when looking at the changes at week

0 in viral load. As shown here, minus 1.3 logs for the low ose, minus 1.1 logs for the high dose, and to put this in erspective, this represents a 95 percent decrease in aseline viral load and this represents a 92 percent ecrease from baseline viral load.

The 2 dose groups also show similar activity when ooking at all time points from baseline out to week 20. 'hat is shown on this plot, which demonstrates similar ctivity, and at week 20 both dose groups have approximately 1.2 log decrease from baseline.

[Slide]

Although there were no differences in efficacy bserved between the 2 doses, there was a significant lifference in safety. That is demonstrated by this Kaplan-Ieier analysis looking at the time to onset for serum reatinine increase of 0.5 mg/dL or greater.

Looking at the percentage of patients out to week :8 demonstrates that each time there is a higher percentage of patients with this abnormality in the 120 mg dose group, and this result is significant, as shown here.

[Slide]

There is a difference as well for graded toxicity with regard to serum creatinine, as shown here, where 3 patients at the higher dose group had a grade 2 abnormality, whereas no patient at the 60 mg dose group had a grade 2 or

higher abnormality.

[Slide]

There was also a significant difference for the development for hypophosphatemia, as shown by this Kaplan-Meier which again looks at the percentage of patients from baseline out to week 48, and again demonstrates that at each time the percentage is higher in the 120 mg dose group and, again, the result is significant.

[Slide]

Looking also at the graded toxicity for hypophosphatemia also indicates, again, a difference, with 23 percent of the patients in the high dose group developing grade 2 or higher toxicity and about 16 percent of the patients in the low dose group developing a grade 2 or higher abnormality of serum phosphate.

[Slide]

The conclusions we can draw from this study are that drug regimens containing 60 mg of adefovir are equivalent to regimens containing 120 mg of adefovir with regard to the proportion of patients with less than 400 copies/ml at week 20.

In addition, changes in HIV RNA are indistinguishable for the 2 dose levels. The 60 mg dose is better tolerated than the 120 mg dose with regard to both gastrointestinal side effects and nephrotoxicity.

[Slide]

From the data collected in this study, as well as studies 408 and 411, we conducted a multivariate analysis looking for risk factors which are associated with the development of nephrotoxicity. There were 4 baseline factors which had either a significant increased or decreased risk for the development of either creatinine increase or hypophosphatemia.

Non-Caucasian patients had a decreased risk for both creatinine increase as well as hypophosphatemia, and these data are also consistent with that reported for study 039.

Decreasing baseline phosphate, as well as increasing baseline age, were both associated with an increased risk for the development of increased creatinine or hypophosphatemia. Supporting the observations in study 417, the higher dose was associated with a 2-fold increased risk for creatinine increase and a 1.8-fold increased risk for hypophosphatemia.

[Slide]

To provide additional safety data for the 60 mg dose, we looked to our expanded access program in which we have administered both dose levels. This is an open-label program in which we registered almost 800 sites and close to 2000 physicians. This group of physicians were responsible

for 70 percent of the antiretroviral prescriptions last year in the U.S.

Through October 4, 9000 patients have been enrolled, including over 3000 at the 60 mg dose level. The analyses I will discuss will focus on the initial 1000 patients that received 60 mg, and this group of patients has a median duration of therapy of 6.1 months with a range out to 16.2 months, and 604 patients have received greater than 6 months of dosing and 43 patients have received greater than 12 months of dosing.

[Slide]

The baseline characteristics for this group of patients is significant with the inclusion of over 30 percent of patients from minorities. These patients have a baseline HIV RNA of 100,000, and these patients were receiving a median of 4 concomitant antiretroviral agents.

[Slide]

Although this study is still ongoing, this Kaplan-Meier shows the time of study drug discontinuation for the 60 mg dose looking at the percentage of patients out through week 48, and indicates that the median time to study drug discontinuation is approximately 9 months.

In order to receive monthly drug supply, monitoring of creatinine and phosphate is required. This has allowed us to assess the development of nephrotoxicity

in the study, as based on the case report forms.

[Slide]

Shown here for serum creatinine, about 3 percent of the patients have developed a grade 2 or higher laboratory abnormality.

[Slide]

Looking at hypophosphatemia, approximately 17 percent of the patients developed a grade 2 or higher laboratory abnormality, and this percentage of patients is similar to what we observed in study 417 for the 60 mg dose.

[Slide]

To summarize our clinical trial results, we observe a consistent 0.3 to 0.4 log decrease, corresponding to a 50 to 60 percent decrease from baseline, in viral load. The anti-HIV activity of triple drug regimens is similar for those containing either the 60 mg or the 120 mg dose of adefovir.

The most important dose-limiting toxicity is nephrotoxicity. However, this can be recognized with routine monthly laboratory monitoring and, importantly, Kaplan-Meier estimates indicate that greater than 95 percent of the patients will resolve following drug discontinuation. The 60 mg per day is better tolerated than the 120 mg per day, and based on the activity is a clinically superior dose.

[Slide]

At this time, Dr. Norbert Bischofberger will discuss our HIV resistance studies.

HIV Resistance Studies

DR. BISCHOFBERGER: Good morning. Ii am Norbert Bischofberger, from Gilead Sciences. Phenotyping and genotyping are becoming increasingly important for the management of HIV-infected individuals and may provide a valuable tool for optimizing drug combinations. For that reason we, at Gilead, have initiated a comprehensive virology program in support of the clinical development of adefovir. Our results indicate that adefovir has a very favorable resistance profile, and our results also highlight the importance of adefovir for the treatment of nucleoside-experienced patients.

[Slide]

In clinical practice resistance to drugs is becoming an increasing problem and a variety of mutations in different classes of drugs is commonly seen. Shown here is the prevalence of resistance mutations in over 5000 clinical samples which were submitted to Virco for analysis during the period of August of 1998 and May of 1999. As can be seen, there are a number of nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, and protease inhibitor mutations.

Among the nucleoside reverse transcriptase inhibitor mutations a change in position 215, which is associated with AZT resistance, occurs at almost 50 percent frequency. A change in position 184, associated with 3TC resistance, was present in greater than 40 percent of all the samples. This is followed by changes in positions 41 and 70, associated with AZT resistance, and changes in positions 69 and 74, associated with ddC and ddI resistance respectively. Not shown on this slide but important to the discussion of adefovir is that the combination of the 215 mutation and the 184 mutation occurred in 25 percent of all the samples, and this is taken from greater than 10,000 clinical samples.

[Slide]

We have investigated the development of mutations which potentially give rise to development of resistance to adefovir. Under the standard laboratory selection conditions, we were able to identify 2 mutations, the K65R and the K70E mutations which gives rise to about 12- to 16-fold and 3- to 9-fold reduced susceptibility to adefovir. The K65R mutation has previously been described as a ddI, ddC and 3TC resistance mutation. The K70E mutation is unique to adefovir. Both mutations are very rare. In our own clinical studies in 219 patients who have been treated with adefovir for between 5 months and 1 year, we have never

observed a K65R mutation, and in only 2 cases, which is less than 1 percent, did we observe the K70E mutation.

Looking at the recent Virco database of greater than 10,000 clinical samples, it is clear that these 2 mutations are, indeed, very rare. The prevalence of the K65R mutation is 0.6 percent and the prevalence of the K70E mutation is 0.1 percent.

The fact that adefovir selects only for 2 relatively rare mutations indicated to us that it could also have a favorable resistance profile. This was confirmed by analyzing a large number of clinical samples and recombinant viruses both by us and by outside collaborators. The only viruses which reduced susceptibility to adefovir are viruses which are high-level resistant to AZT and viruses which contain a multi-nucleoside mutation and, as I mentioned already, the 2 viruses which express either the K65R or the K70E mutation.

However, unique to adefovir, all these mutations revert to close to wild type susceptibility to adefovir where the 3TC resistance mutation is present also. So, viruses which are high-level resistant to AZT in the presence of the 3TC resistance mutation, viruses which have the K65R insertion mutation in the presence of the 3TC resistance mutation, and viruses which have the K65R mutation in the presence of the 3TC resistance mutation all

have wild type susceptibility to adefovir.

Moreover, adefovir also has activity against the multi-nucleoside mutation 4151, and that makes adefovir unique among the nucleosides. Further, it has activity against low-level AZT resistant virus and virus which is resistant to either ddI or ddC due to mutations in positions 74 or 69. If the 3TC resistance mutation occurs in wild type background, the resulting viruses are mildly hyper-susceptible to adefovir.

[Slide]

This increased sensitization of viruses by the presence of the 3TC resistance mutation is shown here. These were 4 individuals who, during the course of therapy, developed the 3TC resistance mutation. Recombinant viruses were constructed at baseline and after development of the 3TC resistance mutation. At baseline these viruses all had AZT associated mutations. However, after acquisition of the 3TC resistance mutation these viruses reverted to close to wild type susceptibility.

[Slide]

Similarly, the sensitivity of viruses containing the K65R mutation, dependent on the presence of the 3TC resistance mutation -- that is shown here. These are 4 clinical isolates from the Virco database, which all expressed the K65R mutation, and they are between 4- to 6-

fold resistant to adefovir. [House audio system problems] ... and the 3TC resistance mutation, and they have close to wild type susceptibility for adefovir. This same phenomenon has also been demonstrated with the T69 insertion mutation.

[Slide]

This favorable resistance and cross-resistant profile of adefovir in vitro also correlates with response to adefovir in vivo. This we were able to show in a virology substudy in study 408 where, in a prospective and blinded manner, 191 patients were selected and their HIV reverse transcriptase was sequenced at baseline and at week 24. During this study, HIV protease inhibitors became commercially available and treatment practices changed. So we chose a set of early enrollees, patients 1 through 90, and a set of late enrollees, patients 252 through 352, to match the overall study population. In the end, we had 180 evalauable plasma samples available.

[Slide]

Patients in study 408 had extensive prior treatment history, and the genotype analysis of this virology cohort confirms this. Patients were grouped into 6 categories according to whether they had no mutations, or low-level AZT resistance mutations, or high-level AZT resistance mutations, both in the absence or the presence of the 3TC resistance mutation. Low-level AZT resistance

mutations and high-level AZT resistance mutations were defined as indicated on the slide.

As can be seen, by far the largest group of individuals, 43 percent, had both the high-level AZT resistance mutation and the 3TC resistance mutation. More than 70 percent of all the patients in this virology cohort had the 3TC resistance mutation present at baseline and only a relatively small part, 8 percent, had no mutation.

[Slide]

Based on the susceptibility of these AZT/3TC resistant viruses to adefovir, we speculated or we expected that patients in this genotypic group would respond to adefovir therapy and this is, indeed, what we found. Of the 180 samples in the virology cohort, 24-week HIV RNA data was available on 155 patients, and their response to adefovir or placebo is shown on this slide.

As you can see, all the patients who had the 3TC resistance mutation responded to adefovir therapy, with a mean change from baseline at week 24 ranging from minus 0.5 to minus 0.77. This was highly statistically significant versus the patients receiving placebo in the same genotypic groups. Importantly, the patients who had 3TC resistance mutation and high-level AZT resistance mutation responded to adefovir therapy also, with a mean change from baseline at week 24 of minus 0.5 logs, and this was again highly

statistically significant versus patients in the same genotypic group receiving placebo.

This is important because it is well-documented that patients in this genotypic group respond poorly to antiretroviral therapy, and it is also known that this genotype correlates with more rapid disease progression. In contrast, and consistent with our in vitro data, patients in this group having high-level AZT resistance mutation without the 3TC resistance mutation showed a response to adefovir which was not statistically significantly different from that of placebo.

What I showed you here is the analysis looking at mean change from baseline at week 24. We have also carried out another analysis looking at DAVG, and the results of that analysis are consistent with this one in the sense that patients in this group, number 6, having 3TC resistance mutation and high-level AZT resistance mutation showed a statistically significant treatment benefit versus placebo in the same genotypic group.

This was our genotypic analysis. We have also carried out a phenotypic analysis where patients were grouped according to a phenotypic criterion. That is, whether their virus was high-level resistant to either AZT or 3TC, high level being defined as greater than 8-fold resistant; low level being defined as less than 8-fold, and

this category obviously includes patients with wild type susceptible virus.

[Slide]

The results of this phenotypic analysis were consistent with our genotypic analysis, and they again showed that all the patients who had virus which was resistant to 3TC responded to adefovir therapy, with about a 0.6 lob change from baseline at week 24. Importantly, this group, number 4, having virus which was high-level resistant to AZT and resistant to 3TC -- as you can see here, these viruses were on average 14-fold resistant to AZT; they were greater than 85-fold resistant to 3TC but they responded to adefovir therapy, with a 0.66 log change from baseline at week 24.

Again consistent with the previous analysis and also consistent with our in vitro data, patients in this phenotypic group which had virus which was high-level resistant to AZT without being resistant to 3TC showed a relatively poor response.

[Slide]

Consistent with our in vitro experience, we did not observe the development of resistance mutations to adefovir in this study but, rather, what we saw was a background of predominantly AZT-associated mutations arising with similar frequency in the arm where adefovir was added

on to background therapy versus the arm where placebo was added on to background therapy. It was 35 percent in the adefovir arm, 42 percent in the placebo arm. We did not observe either the K65R or K70E mutation emerging in this study and, importantly, all the patients in the adefovir arm who develop these background nucleoside mutations responded to therapy, with a mean change from baseline of minus 0.58 and this is statistically significant versus the placebo patients developing these background resistance mutations, which did not respond appreciably.

[Slide]

In summary, these clinical findings are consistent with our in vitro findings, and they point to the fact that adefovir has a favorable profile both with regard to lack of resistance development and with regard to lack of cross-resistance.

Adefovir has shown activity against most nucleoside resistant viruses, including AZT, 3TC resistant viruses. In vitro we make the observation that if the 3TC resistance mutation is added in we see increased sensitivity. We see significant reductions in plasma HIV RNA in patients that have this 3TC resistance and, particularly importantly, in patients that have both 3TC resistance and high-level AZT resistance we see continued HIV RNA suppression in patients developing background

nucleoside resistance mutations. Finally, the development of adefovir-specific mutations is rare.

With that, I would like to thank you and hand it over to Dr. Jaffe for discussion of the Phase IV plans and concluding remarks.

Phase IV Plans and Concluding Remarks

DR. JAFFE: Drs. Toole and Bischofberger have described the results of our clinical and virology programs, demonstrating the anti-HIV activity of the 120 mg dose and the equivalent activity and improved safety profile of the 60 mg dose.

[Slide]

To support traditional approval of the 60 mg dose, Gilead has worked with the FDA to develop 2 48-week confirmatory studies. Each is randomized and placebo-controlled and currently enrolling patients.

Study 415 is an intensification protocol for patients with viral load of between 50 and 400 copies/ml. Study 458 will utilize baseline genotype and phenotype to construct a new treatment regimen in patients who have failed their HART therapy. Adefovir or placebo will then be added, as will 3TC, to each arm to select for the M184V mutation. Time to virologic failure is the primary endpoint of each study.

As for the studies previously discussed, Gilead

will conduct further resistance testing to further characterize the adefovir profile.

We will also study a 30 mg dose to see if anti-HIV activity is maintained and kidney toxicity is further reduced, and we will continue our ongoing longitudinal study of patients receiving chronic adefovir and undergoing intensive renal function monitoring. We will also conduct a Long-term postmarketing surveillance study in 2000 patients.

[Slide]

However, most important to maximizing the therapeutic index of adefovir dipivoxil is our risk management program. This has been developed with important input from over 70 community members and HIV prescribing physicians. Central to the program are education and access, access for all patients regardless of insurance status to monthly laboratory monitoring, and education about the risks of adefovir therapy for patients and their caregivers, including nurses, pharmacists and physicians.

We will build upon the foundation established in the clinical trial program and extend it within an expanded access wherein physicians responsible for 70 percent of the ART prescriptions in the U.S. participated. The program will include a patient medication guide containing lay language regarding kidney toxicity. Treatment and laboratory logs will simplify the tracking of monthly lab

tests and required dose changes. Labeling on pill bottles and reminders at the pharmacy and patient and physician registries will also increase awareness. Preprinted prescription pads with limited refills will also be used.

Additionally, a black box in the package insert will emphasize the importance of baseline and monthly laboratory monitoring, and the contraindications of preexisting renal disease, hypophosphatemia and concomitant use of drugs with nephrotoxicity potential.

[Slide]

Now, turning to the rationale for the accelerated approval of adefovir dipivoxil, recent data from the CDC have documented that HART-associated reductions in AIDS mortality are slowing. This is due, no doubt, in part to the complicated and interrelated problems of viral resistance, drug toxicity and adherence difficulties.

While we all want drugs that are safe and effective for a lifetime of HIV therapy, it is the unfortunate reality that with each new treatment switch the time on that regimen decreases, and the number of viable treatment options declines accordingly.

Consistent with this urgent need for new options, approximately 400 new patients have enrolled on the adefovir expanded access program since its initiation. Patients have taken adefovir because of the expectation of 0.3 to 0.4 log

reduction, SO-60 percent reduction, in their viral load.

[Slide]

Shown here are the results of a meta-analysis conducted on data from ACTG studies which demonstrate the relationship between risk of disease progression and change in HIV RNA at week 24 following a change in treatment. Compared to the risk associated with no change, a 0.3 log decline would be expected to reduce the risk of clinical disease progression by approximately 30 percent.

[Slide]

In conclusion, adefovir has anti-HIV activity against the highly prevalent virus with combined AZT and 3TC resistance. While other drugs retain some activity against these viruses, they too have important dose-limiting toxicities. The availability of adefovir will increase the options for constructing a nucleoside or nucleotide RT inhibitor backbone. It has become extremely common practice today to use these backbones to help protect against the potential development of non-nucleoside or protease inhibitor resistance mutations. By the time a patient makes his or her way to a third or later regimen the number of viable RTI options for such a backbone have become severely limited.

Additionally, the simple dosing regimen of one tablet per day without dietary restriction will help

facilitate adherence. Finally, while dose-limiting nephrotoxicity will limit the duration of adefovir therapy in many patients, it is extremely well characterized and easy to recognize. Unlike the dose-limiting toxicities of other antiretrovirals, the pattern of toxicity is not overlapping and, importantly, even when the toxicity does occur at a dose twice the dose sought for approval, it is reversible in over 95 percent of patients with drug discontinuation according to the Kaplan-Meier estimates.

For these reasons, adefovir will make a valuable treatment option for HIV-infected patients who have an urgent need for new therapeutic options.

Thank you for your attention.

DR. HAMMER: Thank you very much. I suspect that the committee is going to have a fair number of questions, and I think for efficiency's sake we should take a short break now, return for the FDA presentation and then open this up for discussion. So, please, try to return at 10:20, no later than 10:25. Thank you.

[Brief recess]

DR. HAMMER: Please take your seats. We are going to proceed with the agency's presentation and then we are going to open this up for committee discussion and questions. The FDA presentation will commence with Dr. Kimberly Struble's discussion.

FDA Presentations

NDA and Clinical Development Overview and Summary of Efficacy: Adefovir 120 mg

DR. STRUBLE: Good morning.

[Slide]

The FDA presentation will provide an overview of the NDA submission and the clinical development history for adefovir, followed by the summary of efficacy results from 4 trials evaluating adefovir 120 mg. Dr. Greg Soon will then provide the FDA summary of efficacy for study 417, which evaluated adefovir 60 mg versus 120 mg. I will then discuss the safety issues which will solely focus on the development and resolution of nephrotoxicity.

[Slide]

Finally, an FDA summary of the virology substudy from study 408 will be presented, followed by overall safety and efficacy conclusions.

[Slide]

In June of this year, Gilead Sciences submitted an NDA application for adefovir 60 mg once daily for the treatment of patients with HIV infection with clinical, immunologic or virologic progression despite prior reverse transcriptase inhibitor therapy.

[Slide]

Notably, the majority of the Phase II/III

evelopment program focused on trials to evaluate the safety nd efficacy of adefovir 120 mg. The choice of this dose as based on 2 dose-ranging trials evaluating doses of 125 g, 150 mg and 500 mg daily. All these doses showed similar ntiviral activity without evidence of a dose response. owever, dose response was apparent for GI toxicities. 'herefore, Gilead chose to study adefovir 120 mg in Phase a II trials.

[Slide]

During the conduct of study 408, which compared .defovir 120 mg to placebo, nephrotoxicity, associated with hosphate and bicarbonate wasting, was observed in a substantial portion of patients after 24 weeks of therapy. he long-term safety of adefovir 120 mg became a concern. here was consensus at that time that the 120 mg dose had an nfavorable safety profile. In response to feedback from nvestigators and the division, Gilead amended their ongoing la rotocols to require a dose reduction to 60 mg/day. Cherefore, the development plan for adefovir was refocused o evaluate the safety and efficacy of the previously nstudied 60 mg dose.

[Slide]

The NDA filing strategy for adefovir 60 mg is based on the following: 4 controlled trials to establish the activity of adefovir 120 mg; one bridging study to evaluate

the relative efficacy and safety of 60 mg versus 120 mg; and an analysis evaluating the reversibility of adefovir-associated nephrotoxicity. Gilead contends that the 60 mg dose produces comparable activity to the more extensively studied 120 mg dose, but the onset of renal laboratory abnormalities is delayed with the 60 mg compared to the 120 mg.

[Slide]

Based on this, the division would like the committee to focus on 4 major regulatory issues today. The first one, although the 120 mg dose is not the proposed dose for marketing, did the original adefovir development establish efficacy of the 120 mg dose in treatment experienced patients?

Two, with respect to efficacy, has Gilead demonstrated sufficient comparability between the proposed marketing dose of adefovir 60 mg and 120 mg, such that one can conclude that adefovir 60 mg is superior to placebo?

[Slide]

Three, does the 60 mg dose of adefovir provide a safer alternative to the 120 mg dose for chronic administration, and has the safety of the 60 mg dose been adequately characterized?

Finally, is adefovir-associated nephrotoxicity reversible and clinically manageable?

[Slide]

As stated previously, the clinical development of adefovir primarily focused on the efficacy of the 120 mg dose. This does was evaluated in 4 clinical trials. First I will review the 4 trials conducted in treatment experience patients, studies 408, CPCRA 039 and ACTG 359. I will then discuss the fourth trial which was conducted in treatment naive patients, which is study 411. Please keep in mind that Gilead is seeking an indication for use of adefovir in patients with prior nucleoside experience.

[Slide]

For study 408, patients who received stable antiretroviral therapy for at least 4 weeks before study entry, with CD4 counts greater than 200 and HIV RNA greater than 2500 copies, were randomized to receive either adefovir 120 mg or placebo in addition to their background therapy.

The double-blind, placebo-controlled phase lasted for the first 24 weeks, followed by an open-label rollover phase. The primary efficacy endpoints were the treatment effects of HIV RNA and CD4 cell counts as measured by a time-weighted average change from baseline over 24 weeks, or DAVG24. It should be noted that this trial was initiated prior to the division's stated preference for evaluating HIV RNA changes by assessing proportions below an assay limit.

[Slide]

There were statistically significant differences favoring adefovir versus placebo for changes in HIV RNA as analyzed using DAVG24. The mean reduction of 0.28 logs for the adefovir group compared to 0.06 logs for the placebo group was observed. However, there were no statistically significant differences between the 2 groups for CD4 cell counts. The mean increase was approximately 3 cells for the adefovir group compared to a decrease of approximately 5 cells for the placebo group.

[Slide]

This figure shows the distribution of HIV RNA reductions averaged over 24 weeks for patients in study 408. The X axis indicates average HIV RNA reductions, with greater reductions toward the left. RNA reductions for the adefovir groups are in red, and in white for the placebo group.

Overall, the distribution for the adefovir group is somewhat more skewed to the left, toward greater HIV RNA reductions. However, both plots have considerable overlap. There were no statistically significant differences between the adefovir and placebo groups with respect to proportion of patients with HIV RNA less than 400 at 24 weeks. Overall, relatively few patients achieved RNA levels below 400 copies.

The design of this trial, in which patients with

ongoing viral replication added a single drug to background therapy, does not always coincide with current standards of care. Such designs may not be suitable for illustrating optimal use of an antiretroviral agent.

[Slide]

A second study, CPCRA 039 -- the design of this trial was similar to that of the 408 study, and treatment experienced patients were randomized to receive either adefovir 120 mg or placebo in addition to their background therapy. This study was designed to evaluate differences in the rate of death and development of AIDS-defining illnesses between the treatment groups.

Due to reductions in AIDS mortality and morbidity resulting from the general availability of active treatments, the DSMB determined that the study objectives would not be feasible unless enrollment exceeded 4000 patients. Consequently, the study was prematurely terminated due to a projected inability to reach a sufficient number of clinical endpoints. However, HIV RNA and CD4 cell counts were collected and analyzed for all patients enrolled.

The analysis plan did not provide predefined time points for analysis of HIV RNA and CD4. It is also important to note that the executive summary was only submitted to the FDA for review, and we have not reviewed

data from this trial in depth.

[Slide]

According to the CPCRA analysis, the mean change from baseline in HIV RNA at week 24 was a decrease of 0.02 Logs for the placebo group compared to an increase of 0.9 Logs for the adefovir group. The mean change from baseline for CD4 cell count was an increase of 10 cells for the placebo group compared to 6 cells for the adefovir group. Overall, there were no differences between adefovir and placebo with respect to changes in HIV RNA or CD4 cell counts. However, there may be several factors that may have confounded the interpretability of these results, such as baseline imbalances in RNA and treatment changes.

[Slide]

Imbalances in baseline HIV RNA between treatment groups were observed. The median RNA for the adefovir group was approximately 8000 copies compared to approximately 26,000 copies for the placebo group. It is uncertain in which direction this imbalance would bias the comparison. However, in several retrospective analyses of clinical trial data, lower baseline RNA has been associated with better treatment outcomes. In an FDA analysis which adjusted for baseline RNA levels according to those seen in study 408, there were still no differences in the HIV RNA change from baseline for the 2 treatment groups. In addition, there was

a substantial proportion of patients with RNA less than 500 copies at baseline. There were 29 percent in the adefovir group compared to 23 percent in the placebo group. However, a CPCRA analysis excluding patients with RNA less than 500 also showed no differences in RNA change from baseline between treatment groups.

[Slide]

In addition, information was not collected on past antiretroviral agents, and there were also no protocol mandated restrictions on changes in background therapy. The applicant states that at month 2 there were significantly more changes in therapy in the placebo group compared to the adefovir group. Agents such as delavirdine, nelfinavir, and abacavir were classified as "other" and not included in the data analysis as a change in antiretroviral therapy. As a result, data on changes in therapy may be underestimated in this trial.

[Slide]

The third study, ACTG 359, was a randomized, partially blinded trial in HIV-infected subjects with at least 6 months prior indinavir use and with HIV RNA between 2000 copies and 200,000 copies. Subjects had also been on a stable indinavir-containing regimen for at least 4 weeks immediately prior to study entry and had taken less than 2 weeks of prior ritonavir or saquinavir. Subjects were

randomized to receive either the dual PI combination of saquinavir and ritonavir plus either delavirdine, adefovir 120 mg or the combination of adefovir and delavirdine, or patients received the dual PI combination of saquinavir and nelfinavir plus either delavirdine, adefovir 120 mg or delavirdine and adefovir.

The primary efficacy endpoints were proportion of patients with RNA less than 500 copies and changes in CD4 cell counts at week 16. Only the executive summary from this trial was submitted to the agency, therefore, we have not reviewed this trial in depth.

[Slide]

For the three versus three drug factorial comparison, there were statistically significant differences favoring delavirdine over adefovir. For the ritonavir-saquinavir groups the proportion less than 500 for the adefovir group was 19 percent compared to 30 percent for the delavirdine group. For the nelfinavir and saquinavir groups the proportion less than 500 was 16 percent for the adefovir group compared to 42 percent for the delavirdine group. In the pooled PI comparison, the proportion less than 500 was 17 percent for the adefovir group compared to 36 percent for the delavirdine group.

This study demonstrated activity associated with the addition of delavirdine to dual PI regimens but was

unable to demonstrate activity of adefovir in combination with PI-based regimens in treatment experienced patients.

[Slide]

For the four versus three drug factorial comparison there were no differences between the dual PI regimens plus delavirdine compared to the four drug combination of dual PIs plus delavirdine and adefovir. For the ritonavir-saquinavir arms the proportion less than 500 for the adefovir plus delavirdine arms was 27 percent compared to 30 percent for the delavirdine group. For the nelfinavir and saquinavir arms the proportion less than 500 was 33 percent for adefovir and delavirdine and 42 percent for delavirdine. In the pooled PI comparison the proportion less than 500 was 30 percent for the adefovir and delavirdine arms and 36 percent for the delavirdine arms.

Again, there were no differences between the dual PI regimens plus delavirdine compared to the four drug combination of dual PIs plus delavirdine and adefovir. This is important because this study has relevance for the interpretability of study 417, which you will hear about shortly from Dr. Greg Soon. In addition, there were no significant differences noted for CD4 cell counts between any treatment groups.

[Slide]

There was a pharmacokinetic substudy conducted

during this trial in a small number of patients. The individual concentration data has not been submitted, nor reviewed, by the agency. The results of this substudy have been presented previously at scientific meetings. Results from the substudy suggest a drug interaction between adefovir 120 mg and delavirdine. However, the mechanism of this interaction is unknown at this time.

In addition, saquinavir concentrations in this study were lower in the presence of adefovir. Therefore, on the basis of the preliminary results of the substudy one cannot rule out a potential interaction between adefovir and saquinavir. Further investigation is warranted regarding potential drug-drug interactions with adefovir.

Gilead has conducted single-dose drug interaction studies with adefovir 60 mg, and contends that there is no pharmacokinetic interaction between adefovir and saquinavir. However, single-dose studies may not be sufficient to assess interactions that may be arising from metabolic induction.

[Slide]

I will now review this study which evaluated adefovir 120 mg in treatment naive patients, which is study 411.

[Slide]

Any treatment naive patients with RNA greater than 5000 copies and CD4 cell counts greater than 100 were

randomized into one of the following treatment groups in this open-label trial: patients received either adefovir, indinavir, zidovudine or 3TC, or adefovir, indinavir and zidovudine, or adefovir, indinavir, 3TC, adefovir, indinavir and D4T or the control arm which was zidovudine, indinavir and 3TC.

When this protocol was submitted we informed Gilead that this trial was underpowered to serve as a registrational trial. In response to our comments, Gilead increased enrollment in arms C and E, which are yellow on this slide, to enable assessment of comparability between these triple drug regimens.

[Slide]

This slide shows the HIV RNA status at week 20 for all treatment groups, and includes proportion of patients less than 400 and the percent patients with missing values at this time point. In this study of treatment naive individuals the adefovir, indinavir and 3TC arm was comparable to that of the control arm at week 20 based on proportion of patients with HIV RNA less than 400 copies.

However, it should be noted that a substantial portion of patients had missing values, most of which had discontinued from study drug at week 20. There were 23 percent in the adefovir, indinavir and 3TC arm versus 26 percent in the zidovudine, indinavir and 3TC arm.

It is noteworthy that arm C had a numerically higher proportion of patients with HIV RNA less than 400 copies compared to any of the other treatment arms, including arm A which consisted of a quadruple therapy of adefovir. The quadruple therapy arm, which is arm A, was not superior to the control arm of zidovudine, indinavir and 3TC and was numerically inferior to treatment C. However, differences between 3 and 4 drug regimens may be difficult to detect over relatively short time periods, particularly in underpowered studies.

[Slide]

I would now like to introduce Dr. Greg Soon who will present the FDA analysis of efficacy for adefovir 60 mg Erom study 417.

Statistical Review of Study 417:

Adefovir 60 mg vs 120 mg

DR. SOON: My discussion will be on study 417, which is the only efficacy study for 60 mg with at least 20 weeks data.

[Slide]

First, I will review the study design. Secondly, I will discuss the possible biological interaction of the background therapies with adefovir doses. Then I will show how the interaction may influence the interpretation of the efficacy results. Finally, I will discuss these results in

light of the ICH guidance on equivalence trials.

[Slide]

Now, I will first review the trial design of study 417, and 214 protease inhibitor naive subjects were equally randomized to 3 combination groups. The first group is the nelfinavir and saquinavir combination. The second group is the nelfinavir and a nucleoside analog combination. The third group is a saquinavir and a nucleoside combination. Within each combination group subjects were further randomized to adefovir 60 mg or 120 mg. The sample size for each treatment arm is listed in the third column.

In one of the protocol amendments, all subjects were required to stop using the 120 mg dose after the week 16 visit. Even though most subjects already had the week 20 evaluation by the time of this amendment, the longer-term comparison between the 2 doses will not be available. The primary endpoint for this equivalence trial is the percent of subjects whose HIV RNA was below 400 copies/ml at week 20.

[Slide]

The original intent of study 417 was not to serve as a registrational trial. It is important to note that study 417 was launched prior to the recognition of adefovir-associated nephrotoxicity after 24 weeks of therapy. Since the safety of long-term dosing of 120 mg of adefovir became

a concern, development of lower doses of adefovir assumed greater importance.

Issues with the design of this trial include the following: First, the 60 mg versus 120 mg comparison may be confounded by this complex combination regimen.

Secondly, determination of the relative contribution of 60 versus 120 in the context of potent combination therapy may not be possible within 20 weeks.

[Slide]

Now, I will describe the observed response of HIV RNA at week 20. The numbers presented in the body of the table are the percentages of subjects in each treatment arm with various responses. For example, in the combination group 1, adefovir 60 mg, 41 percent achieved HIV RNA below 400 copies/ml at week 20; 39 percent still had HIV RNA greater than 400, and 19 percent were missing.

This can be contrasted with the 120 mg arm in which 43 percent had HIV RNA less than 400; 26 percent were greater than 400; and 31 percent were missing. Missing values almost always come from discontinuations due to Factors such as intolerance or lost to follow-up.

We see that for the combination group 1, the percent of subjects discontinued were higher for 120 mg, 31 percent versus 19 percent, but the percent of subjects less than 400 was similar, 42 percent versus 43 percent.

The second combination group can be similarly described. However, percent with less than 400 was lower for both the 60 mg and the 120 mg arm than in the first combination group.

The third combination group appears to be very different from the other two combination groups. For the 120 mg arm, only 20 percent of the subjects achieved the less than 400 status, much lower than the 60 mg arm and the 120 mg arm. This occurred despite the percent discontinued being similar to other 120 mg arms. It is 31 percent here versus 34 percent and 31 percent here.

[Slide]

The question here is, is there a statistical interaction between the combination regimen and adefovir doses. The default assumption here is that there is an interaction. The hope is that the trial will provide evidence to refute it. A test of this statistical interaction using a logistic regression analysis yielded a p-value of 0.15, suggesting that there is only a small probability of 15 percent that the seemingly different response patterns in the 3 combination groups were due to chance if, in fact, there is no statistical interaction. This raises the possibility of biological interaction between the combination regimen and adefovir doses, which suggests that these 3 combination groups may not be

described by a singled pooled analysis.

[Slide]

This table shows several possible analyses when missing values are treated as failures. The red row indicates the pooled analysis for all the 3 combination groups. This would be a proper analysis if the biological interaction does not exist. Looking at the lower bound of the 95 percent confidence interval, this analysis suggests that the 60 mg dose is no more than 2.7 percent worse than the 120 mg dose.

The yellow rows pooled groups 1 and 2 together but analyzed group 3 separately. In group 1 and 2, the point estimate of the treatment difference is 1.1 percent; in group 3, the treatment difference is 27.2 percent, both favoring 60 mg.

Examining the 95 percent confidence intervals, we see that in group 1 and 2 60 mg could be as much as 14.2 percent worse than 120 mg, while in group 3 60 mg appeared to be superior to 120 mg. Separate analyses for groups 1 and 2 were not conducted because these 2 groups appeared to be similar.

[Slide]

In addition, analysis was done on subjects with week 20 HIV RNA measurements. Essentially, this is an on-treatment analysis where subjects who discontinued by week

20 were excluded. Based on this analysis, in the first combination group the percent of less than 400 was 52 percent versus 63 percent favoring 120 mg.

In the second combination group the percents were 41 percent versus 43 percent, numerically very similar. However, the third group still appears to be very different from the other 2 groups. The percent of less than 400 was 51 percent versus 29 percent, this time favoring 60 mg.

[Slide]

When all 3 groups are combined, again looking at the lower bound of the 95 percent confidence intervals, the analysis suggests that 60 mg could be 11.3 percent worse than 120 mg in achieving the less than 400 status. However, if we believe that there is a biological interaction, then this pooled analysis is not meaningful. If we combine the first 2 groups, then the analysis indicates that 60 mg could be as much as 25.1 percent worse. However, for the third combination group, it was shown that 60 mg is no more than 2.7 percent worse than 120 mg.

[Slide]

Because the case for efficacy of 60 mg is mostly based on this equivalence trial, the criteria for evaluating equivalence are very important. Therefore, we will review the draft ICH guidance on this issue.

Based on this guidance, there are 2 minimum

requirements for an equivalence claim. First, the control arm for the equivalence trial should be an established therapy. Second, the equivalence margin, sometimes called delta, should be less than the smallest effect size expected for the control versus placebo.

Based on these criteria, a minimum goal of an equivalence trial should be to establish the superiority of the new drug versus placebo without actually conducting a placebo-controlled trial.

[Slide]

What these minimum requirements entail for study 417 is that in order to claim equivalence for 60 mg versus 120 mg, first, 120 mg has to be proven to be superior to placebo in treatment experienced patients. Second, the equivalence margin used for this trial should be no more than the smallest effect size expected for the 120 mg versus placebo in treatment experience patients.

[Slide]

There are several limitations in assessing equivalence for study 417. First, activity of 120 mg was not consistently demonstrated in treatment experience patients to serve as a well-established control. That is, only study 408 was supportive.

Second, it is difficult to choose an adequate equivalence margin for dose comparison for study 417 because

of the small treatment differences observed with 120 mg versus placebo in study 408, and the lack of a placebo-controlled study with 120 mg in a comparable population and similar background therapies as study 417.

[Slide]

Now Dr. Kim Struble will return to provide the overview of safety and summary conclusions.

Summary of Safety and Virology Substudy and Overall Conclusions

[Slide]

DR. STRUBLE: The overview of safety for ad 120 mg and 60 mg will solely focused on the development and resolution of nephrotoxicity. This is not meant to minimize the fact that other toxicities were observed during clinical trials. GI toxicities and increases in liver function tests and bilirubin were observed in patients receiving adefovir. These events were similar to those observed for other nucleoside analogs.

[Slide]

The safety data base for the 120 mg dose is comprised of greater than 6000 patients who received adefovir 120 mg in the expanded access program. It should be noted that all patients in the expanded access program required a heavy dose reduction to 60 mg.

The safety database also consists of 666 patients

who received at least 1 dose of adefovir 120 mg in studies 408, 411 and 417. The duration of treatment varies up to 150 weeks, followed by longer-term follow-up. Study 408 provides important long-term data on the development and resolution of nephrotoxicity.

Study CPCRA 039 and ACTG 359 were not included in this overview because these studies were not Gilead sponsored trials and we have not received all the individual laboratory data to review the safety information from these trials in depth.

[Slide]

I will now review the safety information for adefovir 120 mg from study 407. Most of the safety data contained in the NDA is for the 120 mg dose of adefovir. Nephrotoxicity is the most prominent treatment emergent advent associated with adefovir. Severity, reversibility and management are important safety concerns for long-term adefovir administration. Only study 408 provides sufficient long-term on the development and resolution of nephrotoxicity.

[Slide]

Adefovir-associated nephrotoxicity generally occurs aft er 24 weeks of therapy, and is characterized by these laboratory abnormalities: serum creatinine greater than 0.5 increase from baseline; serum phosphate less than

2; bicarbonate less than 16; proteinuria greater than or equal to 2+; and glycosuria greater than or equal to 1+. All the analyses that I will present focus on the onset and resolution of individual laboratory abnormalities.

[Slide]

Definitions for resolution of abnormalities in serum creatinine, phosphate and bicarbonate were based on the variability of these laboratory measurements in patients receiving placebo in study 408 during the first 24 weeks. For each parameter, resolution within 2 standard deviations from baseline was evaluated. The FDA analysis uses the last available laboratory value to determine resolution of laboratory abnormalities. We believe that this analysis provides a conservative estimate of resolution at the end of study, and includes those patients who may have relapsed.

[Slide]

Overall, 61 percent of patients in this trial who received adefovir 120 mg developed at least one renal-related laboratory abnormality. Approximately 10-29 percent of these patients did not have resolution at the last available value of individual renal laboratory abnormalities such as creatinine or phosphate. It appears that in most cases renal abnormalities were reversible. However, some patients will have some renal function impairment. It is yet unknown if these abnormalities will resolve with longer

follow-up.

[Slide]

Gilead has proposed a clinical management program to reduce the risk of severe nephrotoxicity. This program includes patient and physician education, monthly monitoring of serum chemistries and urinalysis, dose modification based on changes in creatinine or phosphate, and oral supplementation for deficiencies in electrolytes such as phosphate or bicarbonate.

[Slide]

However, we were concerned that some patients may develop significant renal injury despite monthly renal laboratory monitoring proposed by Gilead. Our division conducted several analyses to determine the number of patients receiving adefovir 120 mg with significant changes in renal laboratory parameters. These analyses focus on the development of significant changes in renal laboratory parameters by the next monthly study visit.

[Slide]

Overall, approximately 8 percent of patients who received adefovir 120 mg had a peak creatinine that was twice their baseline. Two percent of patients had a doubling or more of creatinine by the next monthly study visit versus no patients in the placebo arm. Six percent of patients experienced a shift of 3 toxicity grades for

phosphate by the next study visit compared to no patients in the placebo group. A shift of 3 toxicity grades was defined as a shift of normal phosphate which is greater than 2.4 to a grade 3 toxicity which includes phosphate levels between 1 and 1.4.

[Slide]

We were also concerned that sustained increases in serum creatinine could signify persistent and cumulative renal toxicity associated with long-term use of adefovir 120 mg. In the entire adefovir development program for the 120 mg dose, a total of 8 patients required dialysis. Six patients who required dialysis were enrolled in the expanded access program, and 2 patients were enrolled in clinical trials, 1 in study 408 and 1 in CPCRA 039.

Also, continued phosphate wasting could put individuals at risk for bone toxicity. To date, 6 cases describing a bone abnormality, such as osteopenia fracture, have been report ed among patients receiving adefovir 120 mg. However, it is difficult to attribute these events to adefovir since the majority of reports document other potential etiologies, such as concomitant medications or traumatic injury.

[Slide]

I will now review the overview of safety information for adefovir 60 mg. It is important to note

that the safety data for the 60 mg dose predominantly comes from one controlled trial, study 417, in the expanded access program, and 108 patients received at least 1 dose of adefovir in study 408. Of these 108 patients, 77 received adefovir 60 mg for 24-48 weeks and 30 patients received adefovir for more than 48 weeks.

The first 1000 patients in the expanded access program were submitted to the division for review. Of these 1000 patients, 561 patients received adefovir 60 mg for 24-48 weeks and 43 patients received adefovir 60 mg for greater than 48 weeks. Since the development of nephrotoxicity generally occurs after 20 weeks of therapy, it is critical to have a sufficient number of patients who have received adefovir for long periods of time, such as 48 weeks, to adequately assess the development and resolution of this toxicity. However, there are only 73 patients who have received adefovir for greater than 48 weeks. It is important to note that a substantial portion of patients who have received adefovir for more than 24 weeks solely comes from the expanded access trial.

[Slide]

Trial 417 provides information on the relative safety of adefovir 60 mg compared to 120 mg. However, there are several limitations of this trial with respect to evaluating the safety of 60 mg versus 120 mg. These

limitations include, one, a large premature discontinuation rate. Sixty-nine percent of patients in the 60 mg group and 85 percent of patients in the 120 mg group prematurely discontinued adefovir by week 48.

Also, there is a lack of long-term safety information for the 60 mg in this study. After week 28 approximately 50 percent of patients prematurely discontinued adefovir due to either an adverse -event, virologic failure or other reasons. Only 30 patients had a week 48 study visit in the 60 mg group compared to 17 patients in the 120 mg group. There are insufficient number of patients receiving adefovir 60 mg for more than 24 weeks in this trial to adequately characterize the onset and resolution of nephrotoxicity.

[Slide]

The discontinuation rate in this trial can be graphically displayed on this slide, which shows the proportion of patients still remaining on treatment over time. The 60 mg dose is in red and the 120 mg dose is in white. After study day 100 there is a dramatic increase in the proportion of patients discontinuing from therapy. It appears that patients are discontinuing from the 60 mg arm at a slower rate compared to the 120 mg arm. However, there are relatively few patients who remain on study at 1 year.

[Slide]

The data suggests that the time to onset for creatinine and phosphate abnormalities are delayed for the 60 mg group compared to the 120 mg group. However, there were no statistically significant differences for the development of renal laboratory abnormalities and resolution of these abnormalities between doses. However, numerically more patients in the 120 mg group compared to the 60 mg group developed renal laboratory abnormalities. It is unknown if the incidence and time to resolution would be similar for both doses with longer-term follow-up and sufficient number of patients.

It is important to note that comparisons between the 60 mg and 120 mg with regard to resolution is difficult because there is a mandatory dose reduction to 60 mg for patients in the 120 mg group.

[Slide]

The overall safety conclusions from this trial with respect to nephrotoxicity are shown on this slide. Due to a high discontinuation rate, an insufficient number of patients receiving adefovir 60 mg for greater than 24 weeks. Given this limited safety database for the 60 mg dose, it is difficult to conclude whether the 60 mg dose is less nephrotoxic than the 120 mg dose. We believe that longer-term data is needed to fully characterize the time to onset, the frequency, and resolution of renal laboratory

abnormalities for the 60 mg dose.

[Slide]

A safety update was submitted on October 5 of this year to the division for review. This update contained limited safety analysis on the first 1000 patients enrolled in the expanded access program for adefovir 60 mg.

[Slide]

Gilead conducted an analysis on the development of creatinine and phosphate abnormalities for the first 1000 patients enrolled in the 120 mg arm compared to the first 1000 patients enrolled in the 60 mg arm. FDA conducted an analysis on the development of significant renal events by next monthly visit. Analysis regarding resolution of renal abnormalities is limited because it is often difficult to obtain follow-up data once a patient discontinues from an expanded access program.

[Slide]

Overall, 18 percent of patients discontinued from adefovir 60 mg in the expanded access program due to an adverse event, of which 69 percent discontinued due to renal events. Overall, 12 percent of patients discontinued for a renal-related adverse event.

[Slide]

Gilead conducted analysis of time to creatinine and phosphate abnormalities for the 120 mg dose versus the

60 mg dose in the expanded access program. The Kaplan-Meier estimates showed that the time to creatinine increase of phosphate decrease is delayed for the 60 mg versus the 120 mg dose, and that this result was statistically significant. From these Kaplan-Meier estimates at 48 weeks, one can assess the proportion of patients who will develop creatinine or phosphate abnormalities. Approximately 40 percent of patients in the 60 mg group compared to approximately 50 patients in the 120 mg group will develop these abnormalities by week 48. However, there is a question whether these differences in the development of creatinine and phosphate abnormalities between the 60 mg and 120 mg are clinically meaningful such that one can conclude that adefovir 60 mg is a safer alternative to the 120 mg dose.

[Slide]

We conducted an analysis to determine the number of patients who would develop significant renal laboratory abnormalities. Approximately 3 percent of patients had a peak creatinine that was twice their baseline. Overall, approximately 1 percent of patients had a doubling or more of serum creatinine by the next monthly study visit; 2 percent of patients had a shift of 3 toxicity grades for phosphate by the next monthly study visit.

It is important to keep in mind that for this

program a patient's next prescription was dependent on receiving renal laboratory measurements. Despite this, approximately l-2 percent of patients will develop significant renal abnormalities such as doubling of creatinine or a shift of 3 toxicity grades for phosphate by the next monthly study visit.

[Slide]

For ad 60 mg there is also a concern that sustained increases in serum creatinine could signify persistent and cumulative toxicity associated with long-term use. During the expanded access program, 2 patients required dialysis. Also, continued phosphate wasting could put individuals at risk for bone toxicities. To date, only 3 cases describing a bone abnormality, such as osteoporosis, osteopenia or fracture, have been reported among patients receiving adefovir 60 mg. The case of fracture in the expanded access program was due to a trauma from a fall, and additional information is still being collected for the cases of osteoporosis and osteopenia.

[Slide]

I will now briefly comment on the virology substudy from trial 408. One hundred and ninety-one patients were eligible for the virology substudy in trial 408. Eligibility was based on 2 sets of consecutively enrolled patients to categorize early and late enrollees.

Both Gilead and FDA conducted analyses for the substudy. The Gilead analysis included 155 patients who had a baseline genotype, baseline RNA as measured by bDNA, and a week 24 RNA measurement. Their endpoint for this analysis was mean change at week 24, which was presented earlier this morning.

The FDA analysis included 180 patients who had a baseline genotype, baseline RNA as measured by PCR, and at least 1 post baseline RNA measurement. The FDA endpoint for this analysis was the mean DAVG at week 24, which was the primary endpoint specified in the overall 408 trial.

[Slide]

All patients were grouped according to AZT and/or 3TC resistant mutations at baseline. Low-level AZT resistance was defined as RT mutations at positions 41, 67, 70 or 210, or any combination thereof. High-level AZT resistance was defined as RT mutation at position 215, with or without other low-level AZT mutations, or greater than or equal to 3 low-level AZT mutations. Finally, 3TC resistance was defined as RT mutation at position 184.

[Slide]

Gilead has determined that in this substudy they have shown that adefovir retains activity against HIV strains that are both AZT and 3TC resistant and that the 184 mutation augments adefovir activity. In the next several slides I will present the FDA analysis of this substudy.

[Slide]

In the FDA analysis of patients with high-level AZT resistance that also had the 184 mutation, the mean DAVG for the adefovir group was minus 0.25 log compared to minus 0.67 log for the placebo group, which resulted in a treatment difference of minus 0.18 and an unadjusted p-value of 0.032. For patients with high-level AZT resistance alone without the 184 mutation, the mean DAVG at 24 was minus 0.086 for the adefovir group compared to an increase of 0.09 log for the placebo group. This also resulted in a treatment difference of minus 0.18 and a non-significant p-value. Notably, the presence of absence of the 184 mutation did not affect the RNA treatment difference between adefovir and placebo. Both were minus 0.18. However, this was somewhat less than the overall difference for the substudy, which was 0.35. Perhaps the clearest result from the substudy is that patients with high-level AZT resistance alone will demonstrate cross-resistance to adefovir.

[Slide]

The FDA conclusions from this substudy are summarized on the next two slides. Exploratory subgroup analyses are useful for generating hypotheses that should be further evaluated in clinical trials. For patients with dual AZT and 3TC resistance, the treatment difference between adefovir and placebo was less than the overall study

population, which was minus 0.18 compared to minus 0.35 logs.

The presence or absence of the 184 mutation did not affect the treatment difference for adefovir compared to placebo in patients with high-level AZT resistance.

[Slide]

In addition, the hypothesis that the 184 mutation augments adefovir activity requires further study. Furthermore, data presented in the substudy was generated with the 120 mg dose. It is unknown what impact adefovir 60 mg will have on reductions on HIV RNA in similar patient populations.

[Slide]

I will now finish my presentation with the following summary conclusions for both safety and efficacy of adefovir 60 mg for the treatment of HIV infection.

[Slide]

Efficacy of adefovir 120 mg has been evaluated in 4 trials. Study 408 showed small but statistically significant differences in RNA over 24 weeks. Two trials, the CPCRA 039 and ACTG 359, were not supportive cf the efficacy of adefovir 120 mg. The addition of adefovir to combination therapy in treatment experienced patients in studies CPCRA 039 and ACTG 359 did not improve treatment outcomes.

Although Gilead has requested approval of 60 mg for the treatment of nucleoside-experience patients, the more compelling study results were found in the treatment naive patients, which was study 411.

[Slide]

The efficacy of 60 mg was evaluated in one 20-week trial, which was study 417. A second 4-week monotherapy study comparing reductions in RNA of adefovir 60 mg versus placebo was conducted. Since this study did not assess the activity and safety of adefovir beyond 4 weeks, it offers minimal support for approval for the 60 mg dose.

In order to determine if the 60 mg dose is equivalent to 120 mg dose, one needs to conclude that the 120 mg dose demonstrated any viral activity in treatment experienced patients. However, the activity of the 120 mg dose was not consistently demonstrated in treatment experienced patients, therefore, making it difficult to assess equivalence of adefovir 60 mg compared to 120 mg in study 417.

[Slide]

Also for study 417, the pooled analysis which was presented by Dr. Greg Soon suggested comparability. However, this equivalence comparison is problematic and complicated by a high discontinuation rate. There appears to be a possible treatment interaction for group 3, which is