this drug. As has been emphasized, it is a different class of drugs. It is once daily and, in many ways, it is convenient to take. So, I think the company should be applauded for developing this. But I would agree with most of the previous comments that it would certainly be desirable to have a more robust database that would indicate that the drug is useful or is active in the patient populations being studied.

I think from the Phase I and Phase II studies and from 408, there clearly is activity, although it isn't clear in my mind that this meets the definition of having two studies with adequate data and adequate follow-up to provide us enough guidance as to how to use it.

So, I don't think that the data about 120 mg, although promising, meet my definition for proving activity yet, and considering the comments that have been made about the toxicity, I think there is a lot to be learned there.

So, clearly if we need a better database on 120 mg, I think indicating that 60 mg is effective is premature based on what we have seen so far.

DR. HAMMER: Thank you. Dr. Hamilton?

DR. HAMILTON: Perhaps an initial editorial comment will explain my position, which is that efficacy has not been satisfactorily established for the 120 mg dose, nor has the 60 mg dose been confirmed as comparable.

The editorial comment includes the following: I am always incredibly impressed with personal testimonies and impassioned appeals for the licensure of drugs. I have no doubt that in those instances those are heartfelt beliefs in every case, and I have also no doubt that there was a lot of substance to the comments. However, we need to revisit what I think the charge of the committee is, which is to critically assess, by means of a systematic evaluation of systematically and scientifically conducted clinical trials. I think that is so important because I think what we are being asked to do is, on the basis of limited and arguably unrepresentative data, to decide whether drugs have some effects and in a very limited and confined arena.

Though everyone does not necessarily share this view, it is my opinion that we are evolving more and more into the need to address not the short-term implications of drug therapy but the longer-term consequences of drug therapy in a disease that is now chronic. Fortunately, we have 13 or 14 drugs that have been approved. Fortunately, there has been a dramatic decline in mortality and morbidity. But now it is a different scenario and we are talking about people taking drugs for year and year and years, and that is great, but I think we need to adopt new strategies to assess the value of those drugs. And, that may be bad news to industry but I think that is where we are

going, and short-term clinical trials I just don't think are stepping up to the plate there.

So, in summary then, as I said at the outset, though there is some evidence for modest antiretroviral effect in a single trial, 408, there is not a confirmatory trial at that dose. By that definition alone, it would not, in my opinion, meet the criteria for efficacy.

The comparison with 60 mg, it seems to me, is confounded by a variety of circumstances, including the complexity of the studies, the possibility of drug interactions, the short term of the trial, and the large number of missing data making pooling of the data suspect. For those reasons, I would not accept efficacy of 120 mg, nor would accept 60 mg as comparable.

DR. HAMMER: Thank you. Dr. Yogev?

DR. YOGEV: Early my career was as schizophrenic as I am with this specific drug. Listening to the personal testimony, one cannot avoid compiling how many drugs those patients were taking and you find out it was six, eight, ten drugs, and in the studies which were presented to us there were not that many drugs. So, I think that the 120 mg does have some marginal effect -- if one can block the other schizophrenic portion of me -- when you are out of desperation trying to use this, it is easier to take a drug that may has some marginal effect, I think that would be a

place where I would say, yes, the 120 marginal effect might be there. But I was not at all convinced that there is any comparability with the 60 mg.

So, I would say that under the public request, and I think when you do a critical review you have to be also somewhat human and not just look to science, this margin would be enough for me in a very rare patient. And, there were 9000-plus going into it, so there were some physicians along the line looking for something that we don't have today. So, if someone can limit it somehow that if you take six drugs or above you can take this marginal, and it is your choice with the addition with all the toxicity that is there, I might say that this marginal might be sufficient for patients experienced, which many of my colleagues and I interpret as taking AZT for more than six weeks -- that is dangerous and I don't think the data are there. So, 120 very marginal, adding toxicity, and the need in a small number of patients probably has a place for this drug, but I am not sure that 60 at all is the right answer.

DR. HAMMER: Thank you. Dr. Mathews?

DR. MATHEWS: Before answering the first question, I think implicit in any discussion of accelerated approval is, is there a population in need of an agent with this drug's characteristics. I think very definitely there is a need. I think that the volume of the expanded access

program clearly indicates that physicians and patients are scrambling like wild to find agents with some activity that can be components of salvage regimens for people with very limited treatment options.

So, having said that, I want to say that I don't think that the CPCRA study can be properly evaluated for efficacy, and a number of comments have been made as to its negative effect, but I don't think that is a fair appraisal of the results and the agency itself has not had access to the full data set, from what we have been told. The ACTG 359 study, I think, is quite problematic in terms of the unanticipated results, the possible drug interactions that weren't anticipated in the company's previous drug interaction studies. So, I think that is worrisome but, once again, that data set has not been fully evaluated.

Based on the Phase I/II studies and the 408 study, there is little doubt in my mind that the drug has modest activity, of the same order of magnitude of agents that were previously approved in related drug classes. So, I would say, yes, there is activity and it is of a modest nature, which other people have said.

Now, with regard to the equivalence issue with the 60 mg dose, you know, I looked with some attention at both the FDA's analysis and the sponsor's analysis of the equivalence trial, and I must say understanding the

statistical complexities of equivalence designs is not easy. However, the point estimates of the drug effect were clearly equivalent or better for the 60 mg dose, and the issue of the statistical interaction between dose and concomitant regimen I think is debatable, and I couldn't come to a conclusion either way from either the sponsor's or the agency's discussion.

So, I am reasonably confident that the 60 mg dose is equivalent to the 120 mg dose. On the other hand, the sponsor's proposed dosing guidelines and toxicity management program uses a 30 mg dose, for which I could see no data at all to support efficacy, and I would have major problems with that as being part of a recommended management strategy if the drug is licensed.

Now, with regard to the toxicity -- oh, we are just talking about question one right now?

DR. HAMMER: Right now. We will come back to questions two and three but let's stick with question one.

DR. MATHEWS: Okay. I think both limited efficacy and equivalence have been demonstrated.

DR. HAMMER: Thank you. Dr. Stanley?

DR. STANLEY: Thank you. Given the advantages of this drug, I wish that I could say that it is ready to be approved but, unfortunately, I think the answer to question one is no also.

Basically, they are asking us to make a decision on efficacy based on one study, 408, and the effect in that study was minimal. I think it was there so I am ready to be convinced, but I need to see at least another study, as is required by the FDA for accelerated approval anyway. We don't have two studies on true advanced patients that need salvage therapy. Study 417 has patients that are PI naive and 411 had completely naive patients. So, I think the company needs to decide, as I think Roger said, how they want to use this drug and then study those patients and provide us with some good clinical data that will support the efficacy of this drug in the population that they want to target it at.

So, additional data that would be necessary to characterize the efficacy of the 60 mg dose, as others have said, I think we need a placebo-controlled trial using the 60 mg and the 30 mg dose, I think 417 is seriously flawed by not having an arm where there was no adefovir used.

DR. HAMMER: Thank you. Dr. Bertino?

DR. BERTINO: Thank you. First, I would like to thank Dr. Hamilton for his very thoughtful comment. He said a lot of the things that were going through my mind.

I think that in terms of my response to the question, I don't believe there is data to suggest that the 120 mg dose is effective. I think that one of the things

that many of us probably were surprised about when looking at 417 was, as Dr. Stanley said -- where was the placebo arm?

So, I would suggest that if the 60 mg dose should be studied again, we probably need a placebo arm, so 120, 60 and placebo perhaps, and look at patients that have received multiple therapies in the past.

DR. HAMMER: Thank you. Most of what has been stated I concur with. My own personal view with regard to the 120 mg efficacy dose, or at least what I would say is antiretroviral activity, that it hasn't been demonstrated -- 1 would agree with Drs. Mathews and Wong that I believe it has if one looks at the 402 and 403 Phase I/II studies, and in the 408 study there is a consistency in the antiretroviral effect, and there are problematic issues in interpreting the 039 study. Everyone agrees that if it is there, it is modest.

I also think the issues of minimal, at best, modest CD4 count rise also raise issues as far as what the ultimate role and efficacy of this drug is. But my personal comment on efficacy of the 120 mg dose is that, yes, it has been demonstrated. I think there is consistency there. Otherwise, one has to try explain, in two of the studies and the larger study, the 408 study, one has to explain why there is that consistency there.

I would just take a step back though and say that one of the problems -- it has been a very difficult day I think for everyone here and on the committee because each study that has come up is subject to issues of interpretation, either in the design stage or the analysis stage, so trying to paint a consistent picture is difficult, and also with a drug that is of this level of antiretroviral activity it doesn't take much to undercut it because we are not dealing with a drug that has an intrinsic 0.5 log reduction.

That being said, I think efficacy at the 120 mg dose, to me at least, is there. On the issue of has comparability been shown between 60 mg and 120 mg, we are really left with a difficult data set to interpret. On the one hand, there is indication to me from the monotherapy 60 mg trial, the 420 trial, that there is activity there, and it looks across study to be about the same in the 0.3, at the most 0.4 log range, that is a study, because of its small numbers, that the agency has said must be taken in a supportive fashion, but at least it is one of the cleanest studies. The direct comparison of 60 versus 120 in the 417 study -- 1 have little to add to what has been stated. Basically, you either can believe it or you ask yourself where is the placebo control that helps differentiate the data because the background therapies make the comparison

very difficult to state.

So, I am left really with a conundrum. I tend to agree with Dr. Mathews that there probably is activity to the 60 mg dose. It probably does cross the threshold of just biologic and assay variability so I would tend to come down mildly in favor of the fact that it is there but can I say it has been conclusively demonstrated? The answer is no because it is based on the 417 study which, because of the design, the discontinuations, the potential of complicating drug interactions leaves us wanting additional data in that regard. So, that is my personal response to question one.

I would like to turn to questions two and three. I think these can be taken together since they both relate to the toxicity issues. I will read both questions and I would ask each committee member to deal with both of them, and then we will move on to the voting question, question four.

Question two states, had the safety profiled of adefovir 60 mg been adequately characterized? In particular, please comment on the adequacy of the available data to provide labeling information regarding nephrotoxicity and its incidence and reversibility.

The third question, to be taken with it in tandem, please discuss the adequacy and feasibility of the sponsor's proposal for renal toxicity management.

I will again start on my right. Mr. Schouten?

MR. SCHOUTEN: I think that patients and physicians are managing this drug. Expanded access program is exposing a lot of people to this drug and its known toxicities, but I would encourage people not to be too paternalistic and say patients shouldn't be subjected to this risk. I am very concerned about a drug that requires someone to come in for monthly laboratory testing for both the patient and the provider. So I see it from both sides. And, I don't think you can say if you don't come in for your lab next month you don't get your drug. I think there are too many contingencies there, and I now there aren't going to be patients coming in for the drug.

I would like to see -- I know we had a lot of stuff to cover today -- some of the issues of rechallenging. We heard some testimony about early supplementation but I think it does have a well-defined safety profile. It is concerning but I think it is easily managed and I don't think that that would preclude licensing the drug. I mean, it is a manageable toxicity profile.

In terms of the sponsor's proposal for management, I would add there is an inconsistency. In one place they mention phosphate of 1.5 and in other places 2.0 for contraindication. I think what they mean is 2.0 in terms of on study, on the drug.

Then, the other issue is that I am concerned about recommending a dose decrease to 30 mg because of the efficacy, and would prefer to see discontinuation while that toxicity is resolving and not 30 mg. Thank you.

DR. HAMMER: Thank you. Dr. Kimmel?

DR. KIMMEL: I did not think from the data that I saw that the safety of 60 mg has been adequately characterized. I was impressed by the very small number of patients who have been followed to 48 weeks, especially since late manifestation of nephrotoxicity is when you see these issues. I think there was not enough time or patients to really evaluate the toxicity profile.

I was also impressed that the management plan for looking at renal toxicity -- there is very little data to say whether it is a good plan or not. We saw very little data about what the effect of monthly management is in terms of outcomes, and I felt that we just really don't have enough information to make the decision about that plan. I am a little concerned about stopping the drug and restarting the drug with very variable intervals.

DR. HAMMER: Thank you. Dr. Kopp?

DR. KOPP: I also have some very significant concerns about the adequacy of the safety data. I will say I found this a very difficult decision, and I certainly understand the position of community physician and patient

who together wish to make the decision whether or not to use it. On the other hand, I think it is our obligation as a committee to make sure that full and accurate information as to toxicity at various doses is available.

Maybe I could digress for just a couple of minutes or seconds on a couple of issues that have been raised. First of all, how useful is serum creatinine to measure renal function? I think everybody is aware that the most precise measures are inulin clearance, which is clearly not clinically practical. It may not be readily appreciated that creatinine clearance is often used in the hospital setting is not terribly accurate and, actually, the Cock-Croft-Gault estimation of glomerular filtration is substantially better.

Having said that, if we use Cock-Croft-Gault that takes into account serum creatinine, patient age and weight, and imagine a 40-year old patient, a male weighing 72 kg, if he has a baseline creatinine of 1, his creatinine clearance is estimated at 100 ml/minute using that Cock-Croft-Gault.

If we imagine now that he develops toxicity such that his serum creatinine rises to 0.5, if you work that out his estimated GFR has fallen to 67. This is actually a geometric progression, not quite the logarithmic progression, but it is important to realize, and this is the point Dr. Feinberg was making earlier this morning, that

relatively modest changes in creatinine represent significant decrements in glomerular filtration. I know that the sponsor is acutely aware of this and certainly has set their limit relatively low.

I will point out for that same man that if his creatinine serum rose from 1 to 1.4, his clearance would still have dropped from 100 to 71. So, significant decrements in creatinine clearance can still come about from relatively modest changes in creatinine.

The second link point to this is that there is a certain amount of renal functional reserve that I think we all realized. That is, you can donate one kidney and the remain kidney hypertrophies and there is no change in glomerular filtration. At some point, as you pass 50-70 percent of renal mass reduction, that ability to compensate, that is, that renal functional reserve has disappeared, and further insult, toxic insult or something else, has tremendous consequences.

In addition, there is a further point where glomerular filtration has fallen probably below 50 where, in some patients, an insidious process of progression renal insufficiency leading to end-stage renal disease goes forward.

So, the question is how do we understand the various changes in serum creatinine, not knowing in many

cases patient weight and age to be able to estimate creatinine GFR?

I guess, as I look at the data, I see that about half a percent of patients getting this drug develop acute renal failure requiring hemodialysis, and about 5 percent of patients, and here the number is a little bit hard to be sure of -- perhaps as high as 8 percent, perhaps somewhat lower than 5 percent but I will use 5 percent for now are going to be left with a fixed renal deficit in excess of 0.5 of serum creatinine. That is a fall in our hypothetical patient from 100 to 70. What does that mean for that patient? I don't think that patient is at risk for progression to end-stage renal disease, and I think that is the good news. But I think we have to recognize that by having given up a certain amount of renal functional reserve that patient is at greater risk should they live long enough and need additional therapies, should they need cidofovir, should they need contrast as one of these patients here did receive, of developing acute renal failure. That is a certain definable risk. It is not an inalterable problem but it is something that needs to be weighed against the benefit.

Another related point is what do we say about the patient whose- creatinine goes up and then comes back down? Can we say that that patient is entirely back to normal?

Unfortunately, we can't say that that patient is or is not back to normal because of this issue of renal functional reserve being very hard to measure. So, I don't want to push this point too hard but I think in the back of our minds we have to worry a little bit about a drug for which 50 percent, perhaps, of the population treated a year experiences significant rises in their creatinine even though most of them, 80 percent, 90 percent or 95 percent return back to normal.

So, in terms of the available safety data, what I would like to see would be, insofar as possible, complete follow-up of patients ideally after 48 weeks, which I see as the plan, 48 weeks of treatment and then 48 weeks of follow-up in the two proposed studies. I think that would give us a much stronger sense of do the final 5 percent get back to baseline, and they may or may not. As far as 30 mg that has been raised, clearly we need to know a lot more about the safety profile of that drug.

Now, in terms of the packaging information, we are being told that these patients are at increased risk for renal failure if they have an elevated creatinine of 1.5 or more and should be excluded. I would raise the issue for the FDA to consider and the committee to consider whether we should be using Cock-Croft-Gault there as well. Again to give you an example, if we had a 40-year old woman, weighing

60 kg, whose baseline creatinine is 1.4, she has glomerular filtration of 51 ml/minute. I would argue that is such a minimal level of renal function that that might not be a good patient to receive this medication.

In terms of the management plan, once renal dysfunction has appeared, I actually it was quite well done and quite well thought out. I thought the supplements seemed quite reasonable. I actually don't have a major problem with monthly monitoring. I realize that some patients do double their serum creatinine or drop their serum phosphate. I am not clear that there is a major risk to the patient. I am a little bit more concerned about a severe acidosis between monthly monitoring. In fact, we have no data about acidosis in study 417. But I am quite concerned about this issue of continuing a nephrotoxin, even at a low dose of 30 mg a day, in somebody who has established nephrotoxicity that is not returning to baseline, a patient who has a 0.2 or 0.3 increment. It is interesting that many of these patients were able to be treated through the episode, and I don't understand that but I think my own initial take is that I would not want to consider exposing a patient to a nephrotoxin, the same nephrotoxin that has caused damage, and certainly not until information on efficacy is there. I think I will stop at that point.

DR. HAMMER: Thank you very much for those comments. Dr. Verter?

DR. VERTER: I pretty much agree for question two with the comments of the previous three speakers, and I don't have any sense of the package insert.

DR. HAMMER: Thank you. Dr. Wong?

DR. WONG: I have nothing really to add.

DR. HAMMER: Dr. Lipsky?

DR. LIPSKY: On the issue of toxicity, I am a little concerned that, again, it is a one dose fits all. I think there are differences in exposure. We have a drug that is primarily eliminated by the kidney, and if one would think to amino-glycosides, is this the way you would handle amino-glycosides? This isn't amino-glycosides but it is another drug that accumulates in the proximal renal tubule, etc.

When you look at the curves of the time to problems with nephrotoxicity in the two doses, the inflection points or the changes are about the same, and one wonders if the exposure in the lower dose group in some of the patients is not comparable to the exposure in some of the patients in the higher dose group. Perhaps therapeutic monitoring could help in avoiding toxicity with this agent and understanding if there is a relationship between concentration dose and the subsequent development of

toxicity.

The other issue of reinstituting the drug, well, if it is an accumulation problem are you just going to postpone the inevitable, realizing that there is a risk/benefit and the inevitable of not having the drug could be worse than kidney damage.

DR. HAMMER: Thank you. Dr. Masur?

DR. MASUR: I concur with the previous speakers, but I think Dr. Lipsky's point is an excellent point. It appears that there is so little known about the pathogenesis of the renal disease that exploring more a pharmacokinetic or pharmacodynamic analysis for toxicity might be very productive.

DR. HAMMER: Dr. Hamilton?

DR. HAMILTON: I too concur with my associates and their concerns about the renal toxicity, but would add that as a clinician taking care of patients and even as an investigator, frankly, it is not this level of toxicity that is of concern to me in this case; it is the efficacy. Heaven knows, we have learned to live with substantial toxicity when there were other issues more pressing at that time. Unfortunately, we don't have that efficacy at this moment. I will defer at that point.

DR. HAMMER: Thank you. Dr. Yogev?

DR. YOGEV: I don't think we have enough on

toxicity. If you look at the curve and how more patients develop a creatinine problem, it doesn't level off even at 48 weeks. So, we need a much longer period of time to see that accumulating.

Interestingly enough, most of the toxicity -- 60-plus percent of the patients developed toxicity between week 20-28 and one wonders should you add a little bit more closer monitoring at that specific period of time which, for some reason, is unique in the two studies that were presented. So, I think I need to see more. Many of the patients are going to use the amino-glycosides, the amphotericin B, and other drugs that are nephrotoxicity. Is there a synergistic effect, no effect? That is another safety issue which was not addressed and one would like to see.

DR. HAMMER: Thank you. Dr. Mathews?

DR. MATHEWS: Well, I agree with most of the people that spoke before about lack of long-term safety data, meaning beyond 48 weeks. On the other hand, I view this drug as sort of a bridge agent for people that need something in the short run that may not have the option of waiting for two years until the next generation comes along. The fact of the matter is that at least half of the people exposed to this drug at the doses currently used aren't going to be taking it for more than a year, based on the

toxicity and other reasons for dropping out. So, the short-term toxicity seems to be reasonably well characterized. You know, when you view it from a pragmatic point of view, who is need of the drug and how long might they need to be in need of it, I don't have as big a problem with it. If I put a patient on this, which I have many times, I would not expect that they are going to stay on it for much more than a year, at best, anyway.

With regard to their monitoring and toxicity management program, while it is well designed, I think there are a number of unanswered issues. For example, they talk about a 7-day window between use of adefovir and other nephrotoxic agents, but anybody who practices medicine realizes you may not have the luxury of a 'I-day window. If somebody on adefovir comes into the hospital with sepsis and has to be put on an amino-glycoside or amphotericin, there is no window. I don't know what the risk is of the drug in that setting. There are other agents that can affect renal function -- nonsteroidal anti-inflammatory drugs, ACE inhibitors. We haven't heard any discussion about those kinds of things. So, I think more would need to be done with the toxicity management to clarify very practical clinical issues.

DR. HAMMER: Thank you. Dr. Stanley?

DR. STANLEY: Yes, regarding the safety profile, I

too would like more long-term data on the nephrotoxicity, but also I keep going to the graph of study 417 and the continual dropouts of patients even from the 60 mg dose, and I just wonder what the nature of that is. Are there other toxicities or side effects that were just not adequately assessed? So, I think we still have a lot to learn about the safety profile of the 60 mg dose.

As far as the proposal for management, I do ask how did we come up with dose reduction instead of cessation of drug? Again, as someone said earlier, I have seen no data to support that recommendation. Monthly monitoring may allow some people to fall through the cracks, as the FDA's analysis pointed out, but I don't see much of a better alternative to monthly monitoring.

I would point out that that is going to be problematic for some of our patients who are perhaps ADAP or Medicaid patients who, to maximize their medication usage, have to rely on getting multiple months at once. So, I think it is going to pose just some logistical problems for certain patients that need to be considered, but I don't see a better alternative at this point.

DR. HAMMER: Thank you. Dr. Bertino?

DR. BERTINO: I would concur with many members of the committee that I would like to see more data on the 60 mg dose from a safety standpoint. I am actually not even

going to comment about nephrotoxicity but talk about some other things. Carnitine supplementation, for example, is recommended and I am kind of sitting here, thinking, well, why? Is there something that has been shown in terms of carnitine levels drops so that we need to supplement carnitine, etc? Does that affect efficacy of the drug? We don't really have any of that information at hand.

It appears that the decision to either reduce the dose or stop the drug -- I am not quite sure from the 60 mg to 30 mg dosage reduction that we saw data today that supported that. So, I don't think that I could support that in the labeling either.

In terms of the sponsor's proposal for renal toxicity management, there certainly is a precedent for this kind of monthly monitoring and that is with the drug clozapine, where patients are monitored very regularly -- in fact, I think it is more than monthly, for white blood cell count, and then once the white count is obtained it is fed back to the pharmacy and the drug is dispensed. We are king of facing a different situation here, however, because if a patient doesn't get their antiretroviral agent, or if they decide they are not going to get any of their antiretroviral agents for whatever reason, because they don't want to go in for monitoring or whatever, that I think is probably at least as problematic, maybe more problematic than, you know,

missing your clozapine for a few days.

So, I don't have a better way to suggest doing it. I think it is pretty ambitious of the sponsor to suggest this type of management. I think there are a lot of other questions having to do with financial considerations that I know the FDA doesn't consider but I think a lot of us at this table are thinking about in terms of the monitoring and getting multiple months worth of drugs, and things like that. So, I think it is an interesting proposal. It will be interesting how it will work in practice, however,.

DR. HAMMER: Thank you. A couple of comments first with respect to question two, the safety profile of 60 mg of adefovir being adequately characterized, I would like to just dissect this quickly. First, I think the description of it, yes, has been adequately characterized, and I think the time of onset is very clearly evident from the time graphs that we have seen with the inflection points between weeks 24 and 28. I think what is not clearly characterized yet is its full incidence. Of course, that depends on your definitions and your thresholds and, as has been already stated, where those curves will ultimately end up and study to study differences make it uncertain. But that is less of a concern to me because with ongoing data collection, one would find out about that I think.

I think the one open question still, because of

the lack of length of follow-up, is the reversibility. So, I personally have no problems with the description of it for physicians and patients with the clear time to onset, and I think we know the ballpark incidence but we may not know the final incidence per se, but the reversibility and the totality of that reversibility over time is still a question. By itself, however, this does not dissuade from the drug's use. I think it has been well stated by my colleagues about the fact that we have dealt with toxicity-efficacy ratios before in other drugs, and when the efficacy aspects of it are there we can handle toxicities.

I think we should also -- at least some of us -- be internally consistent if in other venues we are stating that HIV disease should be managed by specialists in concert with well-informed patients. Then I think that toxicity such as this that has been fairly well characterized, even if its basic mechanism is not fully understood, can be handled by educated physicians. It is just another statement that, in fact, this disease should be managed by people who know what they are doing in concert with excellent patient education.

As far as the adequacy and feasibility of the sponsor's proposal for renal toxicity management, the sponsor has made a very commendable effort in trying to detail this to get at what the best predictors are of full-

blown PRTD syndromes, and teasing that out as far as creatinine elevations and phosphate declines, and the monthly monitoring I think, in a practical sense -- one really can't do better than that and one has to realize that these are just guidelines for management, and there will be variability in their practice and there is nothing that can be stated in a guideline that will be 100 percent adhered to by 100 of physicians and 100 percent of patients. So, I think the general guidelines are very well thought out. My one reservation has been stated before, and that is that we have no data on the efficacy of the 30 mg, and my personal reaction would be, if one starts seeing nephrotoxicity to remove the nephrotoxin until there is data to suggest that 30 mg is efficacious.

Let's move on to this fourth question for the committee. I will read the question itself for the record: Do the provided data establish that adefovir 60 mg is safe and effective for the treatment of HIV infection? I will defer A or B because it depends on what we say. I would ask the committee members to comment on this but to reserve the vote. They can state whatever they wish but we will take a formal vote after everyone has a chance to make a comment, and then, after the vote, we will deal with A or B as put forward to us by the agency. So, I would put question four to Dr. Bertino.

DR. BERTINO: No on efficacy. I think we know the safety profile somewhat but I think we would like to know more.

DR. HAMMER: Dr. Stanley?

DR. STANLEY: No.

DR. HAMMER: Dr. Mathews?

DR. MATHEWS: Yes.

DR. HAMMER: Dr. Yogev?

DR. YOGEV: No.

DR. HAMMER: Dr. Hamilton?

DR. HAMILTON: No.

DR. HAMMER: I think we are taking the vote. Dr. Masur?

DR. MASUR: No.

DR. LIPSKY: No.

DR. HAMMER: Do you want to make comments?

DR. WONG: I will make a comment. Had this come at 120 mg I would have voted yes but at 60 mg no.

DR. HAMMER: Dr. Verter?

DR. VERTER: No.

DR. HAMMER: Dr. Kopp?

DR. KOPP: No.

DR. HAMMER: Dr. Kimmel?

DR. KIMMEL: I am not supposed to vote.

DR. HAMMER: Okay. Mr. Schouten?

MR. SCHOUTEN: I will make a comment first. There clearly is a niche where some people are benefiting from this drug and I think that patients are being penalized because of the poor design of the trial, 417, in my opinion. So, I am torn about what the FDA should do, and we have a situation where a drug is probably kind of a gap filler for a small group of patients who have no other options, and it works against a class of virus so there is evidence that it works against a class of virus that is resistant to AZT and 3TC.

So, I think if there is some way that this drug could be licensed with the caveat that it be used with AZT, with 3TC in people with documented 215 or AZT mutations and the 184 mutation, I think in that setting it is going to benefit people. But if you are asking about whether or not there is proven efficacy that this drug works based on the data presented at 60 mg in the trials we are looking at, then it doesn't.

DR. HAMMER: I will just make a few comments. First, from the perspective of this committee, my view is that this committee has tried its hardest actually to improve access for drugs, and to look for ways to facilitate getting the sponsor and the agency together to get drugs out in the arena because I think everybody here realizes the need for additional therapies and that we are not where we

want to be.

I also think that the sponsor deserves a lot of credit for trying to develop a drug for a treatment experienced population, particularly, obviously, with a lot of drug resistance, and for trying to exploit something that is at least intriguing to us, and that is the resistance mutation interactions, and for promoting an early expanded access program.

We haven't talked about it too much in this discussion but, in fact, the virology here -- if one accepts, as some of us do, the activity of 120 mg and accepts some of the in vitro data vis-a-vis hyper-susceptibility with the 184 mutation and the 408 virology substudy, is one area that is of particular interest. One wishes that that number were greater. One wishes that there had been a trial that actually randomized patients with the 184 at baseline to various interventions to try to prove this. One would also liked to have seen some similar data at the 60 mg dose per se in comparison to the 408 substudy.

I also have to mention that coming into this the virology issues with adefovir and activity against isolates with the 184 mutation and the niche that that holds, that the agency's presentation in that regard casts some doubt on one aspect of that which creates overall some doubt about full interpretation. So, again, it is an area that is

intriguing. I wish that the fact were clear-cut in that regard, but additional data are necessary.

I would echo what Dr. Wong just mentioned, although the toxicity make it incumbent upon the sponsor to reduce the dose from 120 mg to 60 mg, the vote on question four would have been substantially easier for me personally at 120 mg than it is at 60 mg.

With that said, I think we should go ahead and vote. I will read the question again and list the voting members. Do the provided data establish that adefovir 60 mg is safe and effective for the treatment of HIV infection?

The voting members are Drs. Masur, Lipsky, Hamilton, Pomerantz, Wong, Yogev, Mathews, Stanely, Feinberg, El-Sadr, Verter, Bertino, Kopp and me.

So, if you are voting yes on question four, please raise your hand.

[One hand raised]

One vote yes. Those voting no on question four, please raise your hand.

[Show of hands]

I would state for the record that Drs. Feinberg, El-Sadr and Pomerantz left their written votes as no. So, the final vote is one yes and thirteen no.

We will then go on to a discussion of 4A. If not -- and that is the consensus of the committee -- what

additional data should be provided prior to reconsideration of this application for approval?

Rather than going around point by point, person by person, I will open this up for those who want to comment. Dr. Bertino?

DR. BERTINO: Well, I think it will be very important to have drug interaction information in patients with HIV disease, particularly in this case I am curious about things like saquinavir, using multiple doses of both antiretrovirals, indinavir and whatever other antiretroviral agents, and also adjunctive agents that are used for OIs, things like that.

I also think that more data in terms of pharmacokinetics of these agents in HIV patients is important. I think that we saw some data looking at sex and at ethnicity earlier, and it was nice to see that data. But it is becoming pretty clear that HIV patients are not the same as normal volunteers, and one of the speculations is that it is because of cytokine production. So, there may be a need, if you are going to do drug interaction studies to even stratify by viral load, if you want to use that as a surrogate, or actually measure cytokines, which is being done in some centers now because pharmacokinetics and drug interactions may change over time as viral load drops. Pharmacokinetics in children -- I was kind of left with what

exactly -- under the age of two what kind of pharmacokinetic data was available.

I wonder if the drug shouldn't be dosed on a milligram/kilogram basis. I know that may be considered the death knell for a drug but, as Dr. Lipsky pointed out, we may be seeing a dose-response effect and the reason why the 120 mg and 60 mg curves bump up at a fairly similar point for nephrotoxicity may be due to exposure. So, should we look at dosing the drug on a milligram/kilogram basis?

Then, finally, how should toxicity be handled, nephrotoxicity? Should you reduce the dose? Should you stop the drug? Should you supplement? Can you treat through it, etc.?

DR. STANLEY: As we have already said many times, we need a placebo-controlled study of 60 mg as well as the 30 mg. I think it needs to be done in the appropriate populations that this drug is going to be targeted for.

I would also ask for more evaluation of the potential drug interactions. I think it is very suspicious -- the saquinavir and delavirdine results with 120. Perhaps we would avoid that with the 60 mg but I think we need to see more studies on drug interactions.

Finally, in addition to what has already been mentioned, we need to look at the effect of the 60 mg and 30 mg doses on the resistant viruses. Do they have the same

apparently positive results as the 120 mg dose does? So, I think we need some good virologic studies at those lower doses.

I think that the two proposed 415 and 458 are good studies, and we need the data from those studies. That would help tremendously I think.

DR. HAMMER: Dr. Mathews, did you have a comment?

DR. MATHEWS: You know, it is not so obvious to me how, in the target population of treatment advanced patients, you can cleanly do a placebo-controlled study that isn't going to have the same problems that, for example, the 417 study did, where you are going to be comparing it to other drugs that are also active, and not still have the same problems of teasing out confounding by putative drug interactions. So, if any of you have ideas on exactly how this would work -- I am just at a loss to see how that would work.

Secondly, I think increasingly these kinds of studies are going to have to have baseline susceptibility known in advance, and not this business of saving the samples and running them later. I mean, this is not how we practice, particularly for the nucleoside analogs, this drug and others like it. I think these things have to be known up front, and perhaps that is a topic for the discussion tomorrow and the next day.

DR. HAMMER: Comments? Dr. Yogev?

DR. YOGEV: Very quick, I think the company should better define what experienced patients we are talking about, and really find the right niche and not such a vague experienced population because of the toxicity, and I would love to see them also doing some work on pregnant women, especially with a drug which is taken once day which, hopefully, will also be cheaper. Thinking about the international implication of that, maybe they should look into concentrations of the drug in breast milk also as part of that.

DR. HAMMER: Other comments or suggestions? Dr. Masur?

DR. MASUR: I am glad Chris brought up the issue of looking at efficacy because I think it is no small feat to look at efficacy in this kind of population with a single drug. But I think, as Joe and others said, looking at toxicity is something which can certainly be better defined. I guess I would be more comfortable with this drug if it was clear what predicted or correlated with toxicity and how reversible it was if there were less data missing, and it would appear that that data will be forthcoming.

DR. HAMMER: I would just mention a couple of things. I agree completely that the study design issues here are hugely challenging and teasing out the activity of

a single drug is easy to say in the context of this committee and hard to do in practice. But there are a couple of things that one could think about in relation to this drug. One is that when it is added as a fourth drug to a three-drug regimen, while we didn't see data that that made a difference, one could look at early slopes of decline of RNA if frequently monitored and at least get a handle on whether there is a greater potency to the regimen compared to a very acceptable standard of care regimen since depth and rate of decline are predictive of durability. So, one could have an inference there.

I think Dr. Feinberg made the point, since this drug gets selectively stopped often -- in other toxicity areas, because of threats of resistance, we usually stop everything. This is a drug where often it is stopped in isolation and where that is the case, in a more formal analysis of what is truly happening to viral rebound, if it is there, when this drug is stopped, would be an indirect measure but also a helpful measure.

I also think that a prospective randomized trial based on resistance at baseline would have been terrific to see here because, again, the virology could drive the decision-making around this drug. The point, to me, is not just that it has a niche but it has a niche for a particular reason because of the in vitro data and the 408 virology

substudy that suggest that it is active against viruses carrying the 184. One could define a trial based on plus/minus 184 at baseline, then randomized to whether patients need 3TC or something to maintain the 184 in the presence of this. Then with or without an adefovir-containing regimen, again seeing whether you are defining something where adefovir gives you an extra margin of efficacy. So, I think the niche, which is an overused word today, that this drug has allows you to define a study that is virologically based that allows you to look at efficacy.

I think the tortured views that the committee has expressed today are, I think, based on the fact that a lot of us feel there is something clearly here. It may be that with other generation drugs it will be much more clearly there. But one would have liked and wanted to have seen the data to really believe it. I think that one could design a study that is not too large that defines that, and that might have been more convincing to a majority of the committee. But I think that some of those designs that are virologically based can help us tease out the efficacy, and the safety issues have been so well described by others that I won't comment any further on that.

DR. WONG: I guess just to reiterate, I think that the safety issues, the pharmacology, the pharmacokinetics, all of those things -- of course, we need my information but

in my mind the problem was in efficacy of the 60 mg dose. So, if the sponsor could come back demonstrating that the 60 mg dose is efficacious, that would settle it for me.

DR. HAMMER: I concur with those comments. I would also just add that the assay now seems to be available and looked at in primates, a handle on adefovir diphosphate levels at different doses in peripheral blood mononuclear cells would be very interesting to see whether, in fact, there is a dose response or not a dose response with at least relationship to intracellular diphosphate levels and the RNA responses.

MR. SCHOUTEN: I guess my comments are going to relate to the drug-drug-drug interactions and the complexity of assessing that. I don't have any easy solution for that but with a drug that has apparently a fairly flat dose-response curve and an intracellular activation is blood PK data adequate to reassure us that there is not an adverse interaction, and that is a challenge. Particularly for a drug whose purported indication would be for deep salvage, that is even more of a challenge.

DR. LIPSKY: I think I heard that the demand for the expanded use was 400 a month, and you would think, or it should be obvious that that is a desire for efficacy and that one should be able to design a study based on that need and that desire to more formally answer that question.

DR. HAMMER: Any other comments? Dr. Kimmel?

DR. KIMMEL: I think that the data on using the drug after nephrotoxicity is established is very important, and I think renal and virologic parameters should be investigated, and that might give a lot of comfort to members of the committee.

DR. HAMMER: There is one last question which I think we probably have addressed in the ranging comments that we have had throughout the afternoon, but for the record I will read it: What additional recommendations do you have for further investigation of adefovir for HIV?

Does anyone have a comment on that? I think one comment that was made earlier is in the co-infected populations. I think that should be restated for the record. Another very important population is HBV-HIV co-infected individuals.

Seeing no hands raised, I would ask Dr. Jolson whether there are other issues or clarifications you would like the committee to discuss?

DR. JOLSON: Maybe I could just make a quick comment because I think that a meeting like this is difficult for everybody involved, and I think it has been a difficult application for the committee to consider. It has also been a difficult application for our team as well to consider. And, I think that the comments that the patients

made at the open public hearing -- it is hard not to take that to heart, as well as the size of the expanded access program which certainly makes it clear to us that there is a sizeable population out there in need of more options.

Hopefully, the message that I am hearing is that there is something constructive out of this. It sounds like the major issue, as I understand it, is really the standard of efficacy being met in terms of definitively establishing the 60 mg dose and its activity, and that with that type of data, as well as with some of the additional ancillary issues considered, the committee would then feel it appropriate to reconsider the application.

DR. HAMMER: If I could speak for the committee, and please feel free to interrupt if you disagree, although I think there was split opinion on question one, I think the consensus of the committee is that there truly is something here with this drug; that the desire of this committee was to actually believe that there were efficacy data there and to see the data in a fashion that one could feel absolutely comfortable with.

I do think the sense of the committee is that this should not be a closed issue, that further studies and investigation should be performed, and that we applaud the studies that were started because we think that some of those will give us additional answers, and that whatever

additional information can come forward clearly to establish the 60 mg dose as efficacious is the key issue here because that is where the indication is, and the bulk of the information is at 120 but we need efficacy data at 60.

Although much was discussed about what we still don't know about nephrotoxicity, it relates to data collection that is in process or will come about, and in management of it and in patient and physician education. I would at least personally say I don't see that as the show-stopper. I see the issue here coming in with clear-cut demonstration of 60 mg efficacy data that the agency and the sponsor can agree on, such that if it comes before this committee again we have a clearer focus that there is something there. Some of us tried to see it but it was not fully clear to us.

So, I think what you are taking away is that, in fact, we would encourage more information and reconsideration of this agent, specifically with convincing information about the 60 mg dose, and however quickly one can get there is what we would like to see because I think it is obvious that this committee shares the thoughts that were expressed at the open public hearing that we are not where we want to be and that options should be out there for patients and physicians, and that is the position this committee has taken before.

We have an obligation to look at the data and critically review it. Also, under the issues of accelerated approval, there are issues of critically reviewing the information and we are dealing with this individual agent but also, in our minds, we are looking at the history of where we have come from and where we are going in drug approvals for this disease, and critical data analysis is clearly part of that.

So, we would love to see a study that is unequivocal, or at least marginally equivocal, that both the sponsor and the agency can agree shows activity at the 60 mg dose.

Anyone disagree with that lengthy response? On that note then, I would like to thank the sponsor, Gilead Sciences. I would like to thank the guests and consultants on the committee and the members of the committee and the agency, and particularly the FDA presentations today which were clear, and for the audience participation. Thank you. The meeting is adjourned.

[Whereupon, at 5:55 p.m., the proceedings were adjourned, to resume at 8:30 a.m., Tuesday, November 2, 19991

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