1641, please?

[Slide]

Here is an example of a patient who failed without resistance, the single patient in protocol 4 who failed without resistance to any of the agents. What you see is that there was a very rapid virologic response to less than 400 which was maintained for a short time. Subsequently the patient rebounded to about the same point that they had started. We sequenced the integrase gene at that point and there were no changes noted from the baseline sequence at that point. That patient continued on and we subsequently sequenced both integrase as well as the RT gene later, bearing in mind that this patient was on 3TC and tenofovir, and we saw no changes in any of the genes. So, you can draw your own conclusions.

DR. FEINBERG: It looks like a patient who stopped taking his or her medicine.

DR. MILLER: I will take your conclusion. Can I look now at 1642 for a second example?

[Slide]

Here is another example of a patient. This was one of the patients actually who initially did not have any changes in integrase. Again, a very rapid response to less than 400/mL. There was a therapy interruption. When we sequenced that patient both in integrase and RT at the points indicated there, there were no changes evident in integrase. There was a mixture at position 184 indicating that there was a beginning of some selective pressure for 3TC resistance. The patient subsequently resumed therapy but then went on later to rebound again. When we sequenced that patient later, we now saw two mutations in the integrase gene Y143C and S230R, both of which are indicative of raltegravir resistance.

So, I think this is also an exampleB-two things, one that whenever we see patients fail for whatever reason there may be multiple reasons independent of resistance. But when patients are truly on the drug and they ultimately fail longitudinal data will probably show that most of them go on to develop resistance.

DR. FEINBERG: So, in this particular case this happened somewhere around day 700--

DR. MILLER: Yes.

DR. FEINBERG: B-that the patient developed raltegravir resistance. Imagining that the 3TC is the weakest link in the regimen in 004, except for that one patient that I spoke about, one would imagine that this sequence is always 3TC resistance prior to raltegravir resistance, especially since high-level resistance is conferred by multiple mutations.

DR. MILLER: I think the data support that. I think the fact that we saw the emergence of 3TC resistance in all of those patients--

DR. FEINBERG: Except for the one anomalous patient.

DR. MILLER: Could you show 1618, please?

[Slide]

That patient at the top had K65R and M184V. I think all of the patients that had any sign of resistance mutations had a mutation at 184. There were six. Except for the one patient who

never developed resistance to anything--

DR. FEINBERG: Right, and the other patient must have been a switch from efaverenz, the one that doesn=t have M184V.

DR. MILLER: At the very bottom?

DR. FEINBERG: Right.

DR. MILLER: He had phenotypic resistance actually to 3TC as well. It is not shown in this slide, but phenotypically resistant to 3TC as well.

DR. FEINBERG: Then, because the comparator arm he has raltegravir resistance so this is something you crossed over to open-label.

DR. FEINBERG: No, actually this is just in the interest of full disclosure, we actually don=t think the substitutionB-we actually don=t know if it causes resistance but it is a very common polymorphism.

DR. FEINBERG: Okay.

DR. MILLER: So, the fact that we see a mixture of S and M at position 230 is not especially worrisome in my view. S230R, we believe, is a resistance mutation.

DR. PAXTON: Being mindful of the time, we are actually a little over into lunch, Dr. Yarchoan, you were the last person on the list. Would you like to ask a quick question now or would you prefer to wait until after lunch?

DR. YARCHOAN: Whatever. It has to do actually with the pharmacokinetics activity. In the backgrounder you talk about a potential in vitro target of 33 nM and one of the unusual things about this drug is that there is a very wide range of levels, of a thousandfold, which I am not sure any of the information really explains right now. But there is a subset of those patientsB-the lower limit is 12 so there is a subset that on the tail end has $C_{12\text{-hours}}$ that are lower than what is ideally your target level. I wonder if you have looked at that particular subset in terms of activity and, if it is lower, there might be some consideration to having patients check levels, just on the assumption that there are not going to be drugs coming down the line and people would want to really maximize their chances of having an effect.

DR. WENNING: You are correct that there are some patients who are included in our PK/PRODUCT analyses who did have $C_{12\text{-hours}}$ concentrations that were below the IC_{95}. Could we show 1071?

[Slide]

This, again, is just showing the outcome for those. It was a small number of patients, 16 out of the 332 patients who had both PK and PRODUCT data for these endpoints. You can see, certainly, there is no suggestion that that the patients with the 12-hour concentrations less than 33 nM are doing worse than the rest of the population.

DR. YARCHOAN: Did you look at the other drugs?

DR. HAVENS: Yes, what was the OBT there?

DR. WENNING: I don=t have the answer to that question.

DR. PAXTON: I am going to stop there. I think it is time for us to go out for lunch. We have an announcement that Cicely would like to make.

DR. REESE: There is a set of keys found. If you are missing your keys, please check at the back table.

DR. PAXTON: We have one hour for lunch so we would like to see everyone back here by 1:40 so we can start by 1:45.

[Whereupon, at 12:45 p.m., the proceedings were recessed for lunch, to reconvene at 1:45 p.m.

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

DR. PAXTON: As you take your seats, I will mention that we are about to go into the open public hearing session of this committee meeting and I am supposed to begin by reading a statement from the FDA and I will go ahead with that.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual=s presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its products and, if known, its direct competitors. For example, this financial information may include the sponsor=s payment of your travel, lodging or other expenses in connection with your attendance at the

meeting.

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

We have two registered open public hearing speakers today. What we are going to do is, the sponsor has asked for about 10-15 minutes to respond to some questions and to some issues that came up before we broke for lunch so we will have the sponsors speak and then move and ask the two registered speakers to come up after that. Thank you.

DR. ISAACS: Thank you very much. There were three items that we wanted to clarify or respond to that came up in the morning session and I will just briefly run through all three of those items.

The first item I wanted to mention briefly

was the question about clade C virus in the Phase 3 protocols. There were six patients in the Phase 3 protocols who had clade C virus, three in the raltegravir group, three in the placebo group, and the response rate in the raltegravir group was that two out of the three patients had less than 50 copies/mL.

The second question that was raised had to do with the tipranavir data and whether there was evidence of decreased response with tipranavir, and we thought the most appropriate way to attempt to answer that further was to look at those patients with tipranavir-resistant virus who had a GSS score of zero, in which case raltegravir would be essentially the only therapy that they were receiving.

I can=t really show you this on a slide so I will just mention briefly the numbers to you. Remember that the patients who were being treated who had tipranavir-resistant virus are in the position of having no added benefit from receiving the tipranavir but are getting the inductive

effects on the metabolism of raltegravir. So, one could argue that that is actually the worst-case scenario. Then, by looking at the GSS equals zero you are essentially looking at the inductive effect in the absence of anything else that is happening.

So, if you compare that with the control group, which is patients who have no tipranavir in their optimized background therapy and a GSS of zero, there was a 49 percentage point treatment difference between the raltegravir and the placebo group in that setting in the small subgroup analysis. In the patients who were receiving tipranavir but had tipranavir-resistant virus and had a GSS of zero, the treatment difference was 44 percentage points, in that relatively small number of patients. There were 29 patients in the raltegravir group and 12 patients in the placebo group who were receiving tipranavir but had tipranavir-resistant virus and a GSS score of zero. So, the two treatment differences were 49 versus 44, and we do think this speaks to the fact that you don=t need to have a dose adjustment when you

give raltegravir with tipranavir because those treatment results are essentially the same.

Then, the last point that I wanted to discuss was that Dr. Andersen, in a series of questions this morning, seemed to express concerns that the indication was too broad. Can we, please, show slide 95, which is the indication that we have proposed for raltegravir?

[Slide]

I think it is clear from the robust discussion that was going on backwards and forwards that we don=t agree with the position that this indication is too broad. It is an indication in treatment-experienced patients but those patients also need to have evidence of ongoing viral replication so this represents a failure population. We believe it is very important to be able to construct appropriate treatment regimens that are effective for the patients, and that the history of HIV therapies has shown that sequential monotherapy has been used far more often than it should be. So, we do not want to see raltegravir

being put into the position of being used as functional monotherapy. We don=t think that is appropriate for raltegravir or for the patient. The best benefit will come when they use it in appropriate combination regimens.

We believe that raltegravir has features that make it useful beyond just its antiretroviral activity. It is convenient. It can be given twice a day without regards to food. The data in the clinical studies support that the compliance was excellent. And, data that we haven=t discussed today at 48 weeks in the treatment-experienced studyB-it is lipid neutral. It doesn=t require raltegravir boosting and, unlike the injectable agent, the injectable fusion inhibitor, it doesn=t require injections. So, it has convenience features that will be useful for patients who are intolerant of other regimens as well.

I think Dr. Andersen=s specific concern arose from the interpretation of the PSS greater than or equal to 3 data that was in the FDA=s backgrounder and we thought it would be useful to

share with the committee the full 24-week data broken down by PSS score. These data have been shared with the agency but they have not yet had a chance to review the data. Can I, please, have slide 462?

[Slide]

It was suggested to me I should have come up with a much higher number but, I am sorry, it is just slide 462.

[Laughter]

This is the complete 24-week data set so everybody who could have reached week 24 has reached week 24 in this analysis. I apologize that PSS is only 2 or more. I will talk to you verbally about the PSS equals 3 scores once we have briefly gone through this slide. We show three forest plots on this slide. The first is HIV RNA less 400 copies/mL. The second is HIV RNA less than 50 copies/mL and the CD4 cell count is on the most right axis.

Just to familiarize the audience seeing it is just after lunch, in these forest plots the

vertical axis in each of them represents the zero point, and these are treatment difference of raltegravir minus placebo, with the 95 percent confidence interval shown in the horizontal bar. So, if you are to the right of the vertical axis the response favors raltegravir. If you are to the left the response favors placebo. Although these subgroup analyses were not designed for complete statistical analysis, if the lower bound of the 95 percent confidence interval is greater than zero, then the nominal p value should be less than 0.05.

I think there are three points to make on this slide. The first is that there is a tremendous consistency in results across the less than 400, the less than 50 and the CD4 cell count regardless of the PSS score. The second is that there are relatively tight confidence intervals around these treatment differences with the complete week-24 data set. The third is the same observation that was made previously, which is that the raltegravir treatment effect is greatest when the patient has the least amount of active agents

in their OBT. In this case PSS equals zero. But as you increase the PSS score you still continue to demonstrate a treatment effect for raltegravir and, in this analysis, the zero, 1 and the greater than or equal to 2, all of the lower bounds of the confidence intervals exceed zero, suggesting that they have a nominal p value of less than 0.05.

With regards to just strictly the PSS equals 3 number, the treatment differenceB-and I have this just for the less than 50B-was 12 percentage points so, once again, favoring raltegravir. So, raltegravir, despite increasing efficacy of the OBT, continues to add value as you go up in the PSS score, and the GSS results are similar to those.

So, overall, it is our belief that the totality of the data support the indication and support the need for patients to be able to have regimens which contain as many active agents as possible to maximize their treatment response and the longevity of their treatment response. I thank you for the time to be able to make those extra

points.

DR. PAXTON: Thank you. A point of clarification, Dr. Havens?

DR. HAVENS: Well, just since one of those responses was theoretically to a question I asked, I just wanted to suggest that I would be glad to talk to them later since the response they gave didn=t answer the question I asked.

DR. PAXTON: Also, keep in mind we still have a whole discussion session later. Now the registered speakers will come up and then we are going to move to the discussion session and you can bring those up and then we will vote. Matt Sharp will be the first speaker.

Open Public Hearing

MR. SHARP: Good afternoon. I want to thank the advisory committee for the opportunity to speak today. It is interesting that I just discovered that one of my first HIV docs is in the room today, so that was another exciting reason to be speaking today.

My name is Matt Sharp and I am coming up

on my 20-year anniversary of living with HIV. I have been an AIDS activist for over 20 years, and I am now director of education and advocacy at Test Positive Aware Network in Chicago. I am also a treatment writer for *Positively Aware* magazine. I am also a founding member of the drug development committee of the AIDS Treatment Activist Coalition. My statement is available today at the front desk.

For disclosure sake, I want to let you know that I am a consumer advocate for the FDA, having served on the advisory committee for Reyataz and for the blood products committee for the HIV home test. I am on several pharmaceutical company community advisory boards, including that of Merck, and my agency in Chicago receives unrestricted and education support from the pharmaceutical industry. I was also the second person enrolled in the raltegravir expanded access program when it was still called 0518.

Although most of the raltegravir data will speak for itself, I am going to speak to you today about my use of the drug and that will, hopefully,

bring an added perspective to this hearing. I also want to advocate for some elements in the further development of raltegravir and the integrase drug class.

My HIV treatment history cannot be told without saying that I am an extremely fortunate person to be here, speaking to you today after several treatment failures and several close calls with death. There are not many of us AIDS veterans that have survived, and we are lucky, but many of us have that survived have also been very active with their treatment and care and have fought for every new drug. The fight will not end with raltegravir.

My background in HIV started with the desperation days of AZT monotherapy in 1980 when my community was becoming decimated by a frightening and little understood disease. Over the next 19 years my strategy was simply to buy time with any and all of the newest drugs and some alternative therapies as well. As we have learned through better understanding of HIV resistance, many people

were sub-optimally treated with sequential monotherapy due to the way the drugs were developed, and they were offered one by one, and the fact that people just had no other choices for treatment. I would add a new upcoming drug to an older drug regimen even though my T-cells kept slowly moving south. I am one of those who tried everything that became available and have paid the price with a multi-drug resistant virus, yet through determination and hope I have managed to stay alive.

So, fast forward to 2006, I used up all my treatment options. I had recently been treated with Aptivus and Fuzeon. My T-cells began to fall and my viral load started to climb again, clearly an indication that the drugs were no longer effective. I was aware of the Phase 3 raltegravir trials as early as late 2005. But, unfortunately, the Chicago site was not able to open and I had to defer treatment over several agonizing months until the expanded access program started in September of 06. It was a frustrating time for me as I knew I

was once again completely out of options, as I had been many times before. At that point I could have gone ahead and used Prezista as it was my only option at the time, but for the first time I could afford the opt to wait for two drugs I had not taken before that were mostly likely going to be active.

I added Prezista and Truvada to raltegravir in the expanded access program. I achieved an undetectable viral load in less than two weeks, and have experienced almost a doubling of CD4 cells, maintained now almost to a year. It appears my immune system is gaining ground as my T-cells are higher than they have been in 16 years. I have a history of recalcitrant cutaneous warts that have started to literally dry and fall off, clearly a sign of immune recovery. My health is excellent. I am working a full-time job, with a regular gym workout and a very active national travel scheduleB-knock on wood.

For someone with as beat up a virus as I had, the success with raltegravir is a significant

achievement. Since the advent of viral load testing I have never been undetectable, save one week on Fuzeon. My case shows that raltegravir especially if used with at least one other effective antiretroviral drug, is going to save lives.

Merck has listened to the community and provided many mechanisms for inclusion, enrollment and access in the benchmark studies and the extended access program. The benchmark design allowed for experimental agents for the first time, offering people more options but also better data for the company. Ninety percent of those who added Prezista to raltegravir in benchmark went below 400 copies at 24 weeks. Good was done for patients and for the company. It is clear how many people need this drug as enrollment in the expanded access program is over 5,000. As with most other HIV trials, Merck needs to work in better recruitment and retention of women in studies.

We can be assured the sustainability of raltegravir is good for the duration of the 24-week

data, but beyond that there are still some unknowns. We understand that here is a low barrier to resistance and there will be cross-resistance with elvitegravir, the next integrase inhibitor in the pipeline. Since raltegravir is a new drug from a new class there needs to be more understanding on resistance and cross-resistance.

The raltegravir side effect profile appears clean and may offer a safer option in treatment-experienced people where side effects are a common and sometimes debilitating problem. As deliberated today, there is a lot of concern that malignancies appeared early on. Longer-term data should confirm that this won=t be a cause for concern. However, follow up studies need to be supported and carried out by the company to qualify both the resistance patterns and to track longer-term side effects.

One of the biggest obstacles with current HIV therapies is drug interactions. Since raltegravir is metabolized via glucuronidation, it should not have many drug-drug interactions with

cytochrome P450 substrates, inducers and inhibitors, such as the current widely used NNRTIs and Pis.

As we know from past approved HIV antiretroviral drugs, there have been issues with companies committing to follow-up studies and there have been no teeth from the FDA to require such studies. Issues such as cardiovascular complications, kidney disease and lipodystrophy are discovered late in the antiretroviral development process. This is a growing area of concern for people living with HIV as we are living longer and want to see longer-term safety data. A good drug is only as good as the proof that it is going to be safe and effective over the long haul and that doctors will prescribe it correctly. So far, raltegravir looks good and the HIV community can support it as long as the post-marketing commitments are all carried out.

Remaining issues are the understanding of how raltegravir may work differently in different populations. Frequent monitoring of liver function

tests and bilirubin tests are necessary since this is a fist-in-class agent. I already mentioned that more work needs to be done on resistance. There should be a better definition of adverse advents including follow up on the malignancies.

One point needs to be made here that I think is highlighted by my story. It is a very unique time in the history of HIV treatment, with several new agents available for people who have previously had few or no options. People today can afford to wait until they can use another new drug with raltegravir to get the best treatment effect. Doctors should test for resistance and carefully construct regimens that will be the most effective to add with raltegravir. Today we have more time and more options to enhance the most optimal treatment effect.

I am also advocating for as low a cost as possible for raltegravir, especially given the fact that it should be optimally used with other active agents that are likely to be the higher priced drugs. The company should decide upon as low a

cost as possible to ensure people have access to this new successful treatment strategy.

While I am here today to support accelerated approval of raltegravir, I am concerned that after Tibotec=s TMC-125 the HIV treatment pipeline is running low. I urge the FDA to make sure that the raltegravir label reflects this dwindling pipeline by giving clear, concise instructions on how to best use the drug so it is not wasted through misuse. Thank you.

DR. PAXTON: Thank you very much. We will now move to our second speaker, Miss Linda Dee.

MS. DEE: Good afternoon, everybody. I will try and be quick. My name is Linda Dee. I am also from the AIDS Treatment Activist Coalition and the drug development committee. I am also from AIDS Action in Baltimore. I have been on actually the first Merck drug indinavir hearing panel, the tipranavir hearing panel and the maraviroc hearing panel. I have received consulting fees from MerckB-I don=t know, about $5,500B-which have gone to my organization, and my organization also

receives some unrestricted funding from the drug companies.

I have some recommendations that the drug development committee has outlined, but what I thought I would do since, as Matt says, the data speaks for itself, I would like to frame our recommendations within the questions that you have to deal with this afternoon. But first, I think I would be remiss if I didn=t indicate that the drug development committee believes that Merck should be applauded for the expedited drug development plan that they have undertaken with this drug, with the use of investigational agents and I for one, I mean I am particularly excited about that and I believe that from now on we need to have investigational drugs, whenever possibleB-I mean, I know the timing was excellent for that with this particular drug, but whenever possible we need to have investigational drugs used in clinical trials for experienced patients. Merck was able to tease out who did what to who, what the side effects were, and whatever, and this should not be a barrier in

the future and we hope that the agency will require this in the future whenever possible. Also, we love the EAP wherein they enrolled 5,000 patients, for which I won the bet I think for that number. Anyway, we are very, very excited about that and thank them for all the hard work they did in those different areas.

Now, the drug development committee believes that the indication that Merck is asking for accelerated approval should be approved. We believe that there are also payer implications and that a broader indication would allow other patients, besides patients that are three-class drug resistant, to use this drug and they may need it. I mean, they may not have three-class drug resistance but they might have other tolerability issues, whatever. Anyway, for that reason we think that it should be approved as requested.

The additional studies that we would like to see, and I am going to put this firstBonly 13 percent of the benchmark studies were in women. You know, I mean I have been doing this for about

20 years myself and I am really just sick of this, you know. Merck did such an excellent job in this EAP because they really worked at it and, you know, you have to incentivize this stuff for investigators be whom would you enroll? The first person who comes to you, you know, and that is not usually women. So, I think that the agency needs to give some legal guidelines about what is the legal incentive and what is not, and the companies are just going to have to do more than say, okay, these sites have a lot of women and these sites don=t so we will use these sites. Anyway, we need PK studies and safety studies in women.

I would also like to point to the Tibotec GRACE study the Phase 4 study that is meeting its enrollment targets, and we applaud them for that. You know, I would love to see the companies do the PK and have enough women to tell us that it is safe in women and efficacious in women up front. And, unless the agency really beats on companies to do larger studies in Phase 4 and makes them pay for those studies they won=t see the wisdom of

including women early on. Anyway.

We also believe that there need to be PK and safety studies with people with hepatic insufficiency and, you know, people with compromised livers generally because there are so many co-infected people; and PK and efficacy studies in the pediatric population.

So, the risk management, the time, three to five years, you know, we couldn=t decide. Some people on our committee thought three years was enough. Some people thought three to five. I mean, obviously it is not an easy question. I personally would like to see the company look at this immune reconstitution syndrome in naive patients to see what happens in naive patients. You know, wouldn=t it be funny if the idea that the viral load goes down so quickly might be a bad thing. It might be causing immune reconstitution. So, we thought maybe naives would be a good place to look and might give us some good information.

As far as question four about the nucleoside-sparing and the two regimens/three

regimens, you know, a lot of us sat around and tried to decide, well, this study looks better; that study looks better. You know, instead, it might be easier to say let=s do a study of a control arm with three drugs versus a nucleoside-sparing regimen and a PI-sparing regimen and see what we get. The only problem is that, you know, it kind of ended up to be a pretty large study when we got done. But, you know, for naives I think this is important and it is also important for the first treatment failure patients. But so much of that I think is going to depend on what they have already failed on. So, strategy is what we would like to see, how the drugs, especially this drug, should be used in the real world and we are very excited that this drug is so good that we might see a new paradigm in the future for naives and even not highly but treatment-experienced patients.

I want to reiterate what Matt said about resistance being so important and us being at a juncture where we have some new drugs

availableB-Prezista and maraviroc--you know, we think it should be in the label that whenever possible this drug should be used with one and even two new drugs. Put it in the label where docs who are in HMOs or in Peoria-BI always get in trouble because there is always somebody from Peoria. I think it is you. Yes, I remember from last time--

[Laughter]

I am sorry, I just remembered now. I will have to get a new city, right! Anyway, put it in the label. You know, I don=t think that hurts anybody. Whenever possible use it with more than one drug.

I know the sponsor has indicated they are going to do this, but we believe that they should make a point of stressing this with not only patients but with physicians. I mean, you know, we tend to be pushing the envelope in knowing all of this information and, you know, not all doctors have a lot of HIV patients. Not all doctors are following this meeting. A lot of them are too busy. A lot of them-Bwhatever, for whatever

reason, but if it is in the label they will see it I think and we can be more sure of that in any event.

Again, this pricing, you know, we know that it is not the province of the agency to talk about pricing but, you know, we really commend Merck for what they did with indinavir and we believe that drug pricing is completely out of control and we hope that the marketing people that are here from Merck, and we have met with them through the Fair Pricing Coalition. Many people on the drug development committee wear more than one hat. But we hope that they will look at a mid-range protease range or even lower than that. You know, we want to know why ten years later the protease inhibitors cost twice as much as they did when they were first developed, when all the problems had to be ironed out. Now that they are kind of Ame too-ish@ why do they cost more? Well, everything costs more but not twice as much. You know? Anyway, we want to reiterate that to the company while we have them as a captive audience.

And we thank you for allowing us to comment.

Discussion/Questions

DR. PAXTON: Thank you very much. Well, we are now going to move into the section of the agenda which involves discussion and addressing the questions posed to us by the FDA.

DR. HAVENS: Lynn, just to clarify my question to them, can I give them this table to see if they can fill it out? I outlined a table that really solidifies the question that I think was perhaps misunderstood. Is it legal for me to pass a note to the sponsor?

DR. PAXTON: I presume so. Is there a problem with it?

DR. BIRNKRANT: Why don=t you just describe what is in it and then you can pass it.

DR. HAVENS: What is in the note is an analysis of patients who are treated with raltegravir only, looking at an outcome less than 400 or less than 50, and looking at patients given tipranavir or no tipranavir by GSS score by tipranavir resistance or susceptibility, and then

for comparison to see if there is really a difference in the tipranavir-related issues compared to the raltegravir-related issues, a darunavir versus no darunavir treatment group by darunavir resistance and susceptibility or GSS. It is just an outline. The kinetics guys will love it. Is that okay?

DR. BIRNKRANT: Fine.

DR. PAXTON: While they are frantically filling in that table, I think we will move forward with the questions that have been posed to us.

So, the first question they have here is do the available data support accelerated approval of raltegravir for the treatment of HIV-1 infection in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy? If no, what additional studies are recommended?

So, what we traditionally do here is we pose the question and you are allowed to discuss it

for a period of time and then we will move on to the next one.

DR. BIRNKRANT: I would just like to add a couple of comments with regard to the first question. That is, with regard to the patient population that is outlined there, that is, the treatment-experienced population and we feel that the trial population was highly treatment-experienced for the most part, the majority had between zero and 2 of the GSS or PSS score. So, I think we should take a vote on this question, keeping the patient population in mind that was studied in the pivotal clinical trial. Then perhaps we could have a discussion of the definition that would be comfortable to the committee with regard to treatment-experienced.

DR. GORDIN: Actually, I don=t quite understand what you are saying, Debra. In other words, the study population, yes, it was treatment-experienced but it was also multi-class resistant. This word Atreatment-experienced@ could imply anybody who had swallowed one dose of

zidovudine.

DR. BIRNKRANT: In other words, the question being asked is a reflection of the population that was studied in the clinical trials who were highly treatment-experienced with triple-class resistance, etc.

DR. GORDIN: That is how you want us to interpret this or not? I am not quite sure what you are saying.

DR. MURRAY: I think another way you could think about it, maybe to get through the question, is to have a vote on should it be approved for a treatment-experienced population and then maybe afterwards commenting because, I mean, it comes down to really labeling wording and the question is really a thumbs up or thumbs down on, you know, kind of the efficacy and safety supporting approval. So, I think maybe you could consider does it warrant, you know, accelerated approval for the treatment-experienced population and then, you know, once you have decided that maybe you want to give us your suggestions for how you would define

the treatment-experienced population. Because I think every person could have a different definition in mind of treatment experience that might kind of destroy the whole point of the kind of question which is more yes/no. Then, to have later discussion on maybe wording that would be helpful in the label. Does that make sense?

DR. PAXTON: Dr. Havens?

DR. HAVENS: Well, you could do it the opposite way and just define treatment-experienced out of the box as resistant to at least one in each class. I mean, could we vote?

DR. MURRAY: But some people might say, well, you know, you might have some people who are intolerant or because, you know, because of a lipid problem they can=t take boosted protease inhibitors. I mean, there might be other things besides just resistance to take into account. There is probably some intolerability, some other patient factors. You know, the definition could be different.

DR. HAVENS: But those might be independent

of treatment experience actually.

DR. MURRAY: They could, right.

DR. FEINBERG: I mean understanding that, prescribers will be free to do whatever prescribers want to do once this drug is approved. None of these studies were done in a patient population described as resistant and/or intolerant. You know, that is the issue before us so we are trying to impute a conclusion from a null set. You know, that is not who was studied in the pivotal trials.

DR. PAXTON: Dr. Hendrix?

DR. HENDRIX: I was just going to say this question is the one that the agency put before us. Why don=t we answer this and then if we want to make comments on specific restrictions or interpretations, but this would be a good place to start with what you have up there.

DR. PAXTON: Right, and sort of following on a little bit on what Dr. Murray was saying, it sounds like we should just vote on whether or not we would recommend this for a treatment-experienced population, yes or no, and then we can discuss what

we would consider to be our definition of a treatment-experienced population and hone it down. So, if everyone is in agreement with doing a yes or no vote, it might just be simpler if we would go ahead and do the voting on this individual question and then have discussion and then move on to the next question. Does anybody seriously disagree with that?

[No response]

DR. FEINBERG: So, can you just restate it one final time so everybody is exactly clear on exactly what our first vote is going to be, how we are defining that?

DR. PAXTON: Basically, we would be following sort of the question as it is written. Do we support accelerated approval of this drug for treatment-experienced patients. It is not delineated right there what the definition of treatment experienced is but basically on what was presented today, who have evidence of ongoing HIV replication.

Now, I have been told that the voting

procedure has changed a little bit here, and what we have to do is I will ask you to do a hand vote of yes or no for this, and you are supposed to keep your hand up as we go around and everyone gives their name for the record. Then I will allow you to put your hand down and then you can talk. All right? Let=s go ahead and vote. We have read the question now two or three times. Those who vote in support and so vote yes for this, please raise your hand.

[Show of hands]

Keep it up. We are going to start with Dr. Havens on that side. Give your name.

DR. HAVENS: Peter Havens.

DR. PAXTON: Next?

DR. FEINBERG: Judith Feinberg.

MS. SWAN: Tracy Swan.

DR. YARCHOAN: Bob Yarchoan, yes.

DR. GRANT: Robert Grant, yes.

DR. GLESBY: Marshall Glesby, yes.

DR. PAXTON: Lynn Paxton, yes.

DR. McGOWAN: Ian McGowan, yes.

DR. HENDRIX: Craig Hendrix, yes.

DR. ANDERSEN: Janet Andersen, yes.

DR. GORDIN: Fred Gordin, yes.

DR. PAXTON: All right. The thing that we know we are supposed to discuss now is the definition of treatment-experienced. Is there something more that we would like to hone down into? Well, actually, we don=t need to because we all voted yes. So, let=s go further into the question of treatment experience. Is there a particular group that you would recommend this for, or do we need more studies to address that issue? Dr. McGowan?

DR. McGOWAN: Lynn, I just think we are going to be here till midnight because I suspect going around the table we are all going to come from different places. I mean, I would be coming from the direction which is to give clinicians the therapeutic latitude to use the drugs they think most appropriate for their treatment-experienced patients. I mean, we can get sub-nuance of that into all sorts of different variables but, as has

been alluded to, you know, it could be patients who are intolerant. It could be patients where there are some kinetic interactions. There is a whole range of things. Also, I feel uncomfortable about restricting the label to mandate genotyping and phenotyping. There may be instances where that is not possible or desirable. So, my perspective at least is that there clearly needs to be education and studies, additional studies. This is accelerated approval. We are going to learn more about how to use the drug from analysis of ongoing studies. I don=t think we should be so prescriptive in the label. That is my opinion.

DR. PAXTON: Dr. Hendrix?

DR. HENDRIX: I think the way this question is posed the label is usefully vague and clinicians can use this in ways that they need to and additionally provide some latitudeB-well, some room for third-party payers to be able to approve this. So, I think it is an important amount of breathing room. It is not precisely as the studies were done. The studies were probably not done with the

intention, nor did FDA have the intention when the studies were agreed to that it would be so highly restricted to, you know, triple-drug resistant patients. It would be difficult to define that all over again so I think it needs to have this degree of vagueness for clinicians to make their own treatment decisions.

DR. PAXTON: Dr. Grant?

DR. GRANT: Yes, I also agree with the broader indication. Tying it to three-class resistance could put clinicians in a situation where they have to burn through the non-new class in order to get to this drug and that is exactly the wrong thing to do. In fact, I agree that the label should be very specific about needing to protect this drug with at least one, ideally two other active drugs. And, to the extent that clinicians can strategize with their patients to preserve classes so this drug can come on board when it is protected in a fully active regimen is the ideal situation, and requiring triple-class resistance would defeat that purpose. I agree with

the broader indication.

I would also add that the data presented today show nicely superiority in people with triple-class resistance but it also showed non-inferiority in people with GSSs and PSSs of 3 or more, and there is even protocol 004 showing some preliminary hints of activity in naive patients. So, you know, I think given the safety profile and the broad therapeutic window of this drug, a broader indication is warranted by the data.

DR. PAXTON: Did you want to say something, Dr. Feinberg?

DR. FEINBERG: Well, I guess I will speak to the other side of that. Actually, I am always somebody who is very much concerned and committed to the concept of access to medication for patients who need it, but I have some inherent discomfort in describing the indication for a drug as being as far off as this seems to me to be from the patient population that is studied. Now, granted, there are studies in naive patients ongoing so that the

full label will ultimately no doubt read quite a bit differently than the label for this accelerated approval.

But in the minds of people, for example, who would think treatment-experienced is people failing their first regimen, then for the sake of argument, for a patient failing Atripla, since there is nothing simpler than one pill once a day and the most likely reason people fail this is because they don=t take it, then moving to this amazingly potent drug, which is a twice a day regimen, and after you fail Atripla you probably have an M184V so you are rapidly sort of moving yourself into a regimen that is likely to be twice a day for most of the elements. Then, how that is going to be a treatment advance and not just a way to develop a lot of raltegravir resistance in the population is a little worrisome to me. I live in a community where we already have transmitted efavirenz resistance. We have a proportion of patients who come to our clinic bearing a K103N virus. I would hate to start seeing bearing the

three different pathways to raltegravir resistance before they have ever seen raltegravir.

So, I actually think that, you know, it would take some word crafting to get around it, but I don=t think it seems right to me, based on the data sets we have in front of us, to have treatment-experienced and let that be defined loosely as a first regimen failure. I think that is a disservice at the public health level as well as to individual patients. You know, really people can do with their prescription pads whatever they choose to but I don=t know that it is right to transpose these data into a patient population in which it wasn=t studied. So, to me, the wording would have to be highly treatment-experienced if you want to just stay in the treatment-experienced realm. Because if you look at these studies everybody had a range of 7 to 12 years worth of therapy, which always translates into having failed multiple drugs and never just a first regimen. Or, you know, you could use the wording that was actually used in these protocols but, for all those

reasons stated, I don=t think it is a good idea to make a Pandora=s box out of this.

DR. PAXTON: Dr. Gordin?

DR. GORDIN: I feel somewhat similarly. I would prefer to see the wording highly treatment-experienced. I actually don=t think it has to be as restrictive as the protocol. I would be comfortable with a word like multi-class experienced or intolerant but somehow implying that at this stage, in terms of labeling, that is where it was studied. But, again, I will come back to only 134 patients have had 48 weeks of therapy. So, there is a lot to be learned. This seems like an extremely exciting drug that obviously may be useful in many ways that we don=t know today, but in terms of what we have to evaluate it on today I do think it needs to be more restrictive.

DR. PAXTON: Dr. Glesby?

DR. GLESBY: If I could follow up on Dr. Feinberg=s comment about resistance and in the community, it is not clear to me I guess that being more restrictive in the labeling would necessarily

lead to a lower likelihood of developing resistance to this drug. In fact, it could be the opposite if people are waiting too late to use it and not pairing it with other drugs that are sufficiently potent then it could be sort of the opposite of your intended effect.

I would just also like to make the point that compared to other drugs that are available, I think overall based on the data that we have seen today the risk/benefit ratio seems fairly favorable to me, and I think this drug could be quite a reasonable option for people, in contrast to some of the other drugs that we might be using in this population.

DR. PAXTON: Miss Swan?

MS. SWAN: I am wondering if there is another way to go about the language on the labeling, which is leaving the indication broad but specifically stating this drug has not yet been studied in populations other than highly treatment-experienced. I know there is a naive study ongoing. That can be addressed somehow. But

at least so that is right up front and when people are sitting there, making the decision whether to use it they know it is best to be used with other active drugs, best to be used in context of resistance testing, and that the data are limited-Bin one simple sentence that a busy prescriber and a patient can clearly read.

DR. PAXTON: Dr. Havens?

DR. HAVENS: I think I agree with Drs. Hendrix and McGowan in this regard that the more restrictive we are here, while it may potentially protect some people, it would have the negative effects of limiting use perhaps to people who needed it and be over-interpreted by payers or other people. So, we need to be a little bit careful to not over-write this or we may find we are in a position we don=t necessary want to be in.

DR. PAXTON: I am actually kind of agreeing. I think we could be here, as Dr. McGowan said, all night sort of trying to wordsmith this based on the data that we have. I have heard a clear suggestion about perhaps adding the word

highly experienced to this as some indication that it shouldn=t be used, you know, just at the drop of a hat. But I would think we might want to just keep it relatively broad. Dr. Feinberg?

DR. FEINBERG: I would like to ask the agency, you know, there have been a number of drugs recently approved whose accelerated approval was based on very similar patient populations. So, the wording for darunavir, tipranavir, enfurvitide and maraviroc is relatively consistent with how the drug was studied or came from a position of Afeel good.@

DR. BIRNKRANT: I don=t think it came from a position of Afeel good@ but, rather, it reflected the patient population who was studied, and we can mirror that with this drug as well. And, we have ways to handle things in the labeling to somewhat restrict the indication or give practitioners an idea of which populations were studied and which weren=t so we can use wording such as safety and efficacy have not been established in the following patient populations, pediatrics, naive, first

treatment failure, etc.

DR. FEINBERG: Thank you because it is my understanding that for the indications for those other drugs I named the verbiage is closer to the way they were studied, and while I think this is a really terrific drug, raltegravir, I am uncomfortable with departing from a four- or five-drug prior track record of accelerated approvals based on salvage therapies and having the language be wide open. I think part of that is that the purist in me is uncomfortable with stating something that we don=t yet know. We can impute, and we sure hope it is true and further studies may prove it to be true, but it is hard for me as a former and now recurring guest member of this committee to vote for something that I have seen no data on.

DR. PAXTON: I might suggest to the FDA, do you think you have heard enough here? Clearly there are reservations on the part of the committee and I think that we can look to what you have done in the past with other drugs to come up with the

wording.

DR. BIRNKRANT: We are satisfied with the discussion on question one.

DR. PAXTON: So, let=s move on to question two. Number two is if you voted yes to this, what additional studies would you like to see undertaken as post-marketing commitments? Dr. Feinberg?

DR. FEINBERG: Well, for this one I would really like to see studies done in non-clade-bearing patients because the numbers were very small but the confidence intervals were close to or just a little overlapping zero in that patient population, and non-clade B virus represents a huge proportion of the individuals in this world who have HIV so I, for sure, would like to see that.

I would also, as a part of studying that, want to know about resistance development that is clade specific, you know, because we need to know how different HIV viruses are going to respond to this drug. Let me yield the floor to other people, I have other ideas though.

DR. PAXTON: Dr. Grant and Miss Swan?

DR. GRANT: Well, it is the same old story. I think we demonstrate safety and efficacy in white men and then extrapolate to the rest of the world. In this case at least we are talking about an antiviral drug rather than an anti-host product drug. But, still, I think the challenge still stands. You know, we know that 80 percent of this epidemic is occurring in Africa and there were no Africans in this study in the Phase 3 program. We know that 50 percent of the people living with HIV in the United States are Black Americans and I gather only 14 percent in the Phase 3 program were Blacks.

I think on the issues of subtype, to be sure, there is no a priori or mechanism for explaining why different viral subtypes might respond differently to this particular agent. However, the point is that the Phase 3 program, a robust Phase 3 program should recruit a representative sample of people who might use the drug and we have consistently failed to achieve

that. So, you know, I think that the best solution to this is for these trials to be structured in such a way that there is stratified recruitment of people in each of the significant racial and sex groups so that the protocol is assured of studying in the Phase 3 program a representative sample. Absent that, I think post-marketing studies that focus on African populations and Black Americans are clearly warranted.

DR. PAXTON: Miss Swan?

MS. SWAN: I agree with the previous two speakers and support what they have said. I would like to also see more characterization of resistance so it could be clearly ranked. Is it like an NNRTI? Is it like 3TC? Just some sort of rule of thumb for clinicians. HIV-2 in vivo rather than in vitro. Treatment strategy studies that clearly look at this drug in second-line therapy. Blood, brain and CNS penetration. And, I think looking at people by CD4 count when they are treatment naive to see if there is another signal about malignancies or other problems is going to be

really important as well. Thank you.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: Basically, Dr. Grant said what I was going to say, which is I really think that in post-marketing for future studies, not even post-marketing per se, as well as future studies that are looking at drugs like this need to have targeted accruals to make sure that they are happening up front.

DR. PAXTON: Dr. Gordin is next.

DR. GORDIN: I would mention again the tremendous TB-HIV epidemic worldwide and the need to understand how to use these drugs with all the various potential conflicting TB agents, the erythromycins.

DR. PAXTON: Dr. Havens?

DR. HAVENS: Can I ask the applicant how many patients were under age 25 in the current study? The indication is going to be for patients between 16 and 65 or 18 and 65.

DR. ISAACS: I cannot specifically tell you how many patients were under the age of 25 in the

studies.

DR. CONNELLY: Actually, pre enrollment in the Phase 3 studies it was 16 or older. I can=t comment on 25 or less. I can say that there were six patients enrolled in Phase 3 who were 18 and younger.

DR. HAVENS: So, there were six patients between the ages of 16 and 18 and the drug will be approved in that age group based on data on those patients, and then between 18 and 25 we have no idea how many patients were in that age group, where there might still be developing kinetic differences.

DR. ISAACS: We will try and get that information before the meeting closes today.

DR. HAVENS: Then it might be useful to do specific studies in those patients since there are some changes, for example with atazanavir, that accrue at least till age 21, for example.

DR. PAXTON: Dr. Hendrix?

DR. HENDRIX: Just a small comment, it is very unlikely that there are going to be any

pharmacokinetic differences in 16 to 18 versus the rest of the population. You know, it is the little ones that you are going to be taking care of where there are changes, but you are not likely to find variation there, certainly not important relative to the overall variation in the studies.

DR. HAVENS: Well, unboosted atazanavir certainly till age 18 has fairly dramatic differences in kinetics.

DR. HENDRIX: But, again, looking at all the variability that exists in the larger population it is unlikely that those kinds of changes are going to have much of an impact at all, given how robust this is in terms of the concentrations that are achieved and that over the wide range they still have a virologic effect.

DR. HAVENS: Which brings up the other study that I would really be interested in, which is to better understand whatever kind of kinetics or cellular measurement of drug activity is best associated with clinical outcome.

DR. PAXTON: Dr. Feinberg?

DR. FEINBERG: I yielded the floor before but I just really want to reemphasize that I think studies in women in other geographic areas of the world and in racial and ethnic minorities here in the United States I think are really imperative to do. You know, people have mentioned various mechanisms by which you can insist that certain populations be included in a study.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: I feel a lot more comfortable now than I did when I came here that the malignancies that were seen appear to be sort of a random blip, but given that they were seen I think it is important to try to do as many comparative studies as possible. They occur in AIDS patients without any antiretroviral therapy and it is relatively hard to see any drug-induced toxicities against a background of that same adverse event.

The other things I would like to see are some additional analyses of those patients that have low levels to see whether there should be any

specific advice about testing levels and boosting in those patients, and then interactions with other drugs. There is obviously a lot of potential information there that can be gathered.

DR. PAXTON: All right, there have been a number of additional studies recommended. Does anyone have any others they would like to add to the list? Yes?

DR. BIRNKRANT: I would like to ask a question. Even though the product is minimally renally cleared, does the committee see any benefit in conducting a study in those subjects greater than age 65 because the database has only approximately nine who are older than 65. So, if we could get feedback on that?

DR. FEINBERG: I think the minimal renal clearance kind of speaks for itself. I wouldn=t see a necessity to study the PK in older individuals for that reason. You know, whether there are differences in metabolizing enzymes with age, PGP with age, that I don=t know.

DR. YARCHOAN: The other thing is people

over 65 may be on a number of other drugs that generally aren=t found in AIDS patients and you might come up with some unexpected interactions. I seem to be recallingB-I may be wrong in this but probenecid for example has some interactions with other drugs that are metabolized by glucuronidation and there may be some other drugs that are just unexpectedly interacting.

DR. PAXTON: Dr. Grant?

DR. GRANT: The PK studies with the anti-TB drugs I think are critical. Someone mentioned that before.

DR. PAXTON: Did you get your question answered? All right. Well, if there are no further suggestions from the committee members we can move on to the third question, which is the applicant is proposing a risk management plan for raltegravir, including a routine pharmacovigilance plan, ongoing clinical trials, a pregnancy registry, and an active surveillance program. The duration of the active surveillance program is at least three years post-launch. Do you find this

duration period acceptable?

Well, as an epidemiologist I can=t stop myself, I have to say a lot depends on how fast you accrue into this. So, to a certain extent, you know, three years is likely to be a minimum, but if you are not accruing very rapidly you would have to definitely extend it as it is. I usually tend to think in terms of what kinds of numbers would you need to see and how long do you think you would get them in. Miss Swan and then Dr. Feinberg.

MS. SWAN: Given that it is a completely novel class of drugs, I think five years would be great.

DR. PAXTON: Dr. Feinberg?

DR. FEINBERG: Yes, I concur. I think a longer period of observation, (a) for the new mechanism of action but, (b) also to get greater clarity on the malignancy issue which I think you need a longer time period of observation for.

DR. PAXTON: Generally a good rule of thumb is longer is better. Dr. Grant?

DR. GRANT: Not so much on the duration,

but I would want some assurance that the surveillance program is truly active. I think just calling it active leaves it ambiguous as to exactly what they are going to do to make sure that all pregnancies are tracked and that there is active surveillance for malignancies, which I think are the two areas of missing data or areas where we need more information. Three years could be long enough if I was really convinced that these programs would be active and that events in everyone taking the drug would be captured in the databases.

DR. PAXTON: Any other points of view?

[No response]

Good. So, overall, longer is better. We are hearing that five years would be at least a good target to go for.

Number four then is please discuss the pros and cons of the following potential treatment strategies in future clinical trials used to support drug development, and more specifically, if you would like to see these studies conducted using

raltegravir as post-marketing commitments.

We have (a) nucleoside-sparing regimens in treatment-naive patients using either two-drug/two-class or three-drug/three-class regimens, or (b) nucleoside-sparing regimens or three-drug/three-class regimens in first treatment failure patients. Dr. Glesby?

DR. GLESBY: I guess the way these questions are worded implies that the nucleosides in a first-line regimen would be the biggest concern in terms of presumably toxicities, and that is what this is getting at. I guess in the era of commonly used first-line nucleoside drugs I think you could just as easily substitute a different class, whether it is a boosted protease inhibitor, maybe potentially non-nucleosides. So, I guess I am not sure I am understanding why the focus is on nucleosides in this particular question.

DR. PAXTON: Perhaps the FDA could clarify that.

DR. MARCUS: Treatment-naive studies currently continue to utilize nucleosides as

background regimens and we are collecting that type of data in treatment-naive patients with drugs under clinical development. So, we would like people to consider alternative regimens, nucleoside-sparing being the first to come to mind because it is the anchor that is being substituted in current development programs.

DR. PAXTON: Shall we perhaps talk about (a) first? Dr. Feinberg?

DR. FEINBERG: Actually, I think it would be a useful thing to look at nucleoside-sparing regimens. They seem to be responsible for many of the long-term toxicities that are of most concern to patients and some of the scariest ones to clinicians. But I would actually rephrase this sentence to say I would actually study two-drug/two-class in a placebo-controlled manner with three-drug/three-class.

The concept that we need three drugs is really a historical accident based on what drugs with what mechanisms became available over time. So, I don=t know that I am convinced that it is

impossible to have a solid, durable two-drug regimen, you know, depending on the class and the mechanism of action, and I think that is a reasonable thing to look at, especially for people who are starting therapy, you know, are new and they are going to be taking therapy for the rest of their life. So, I think that is a very valid thing and they didn=t show that data today but it is very impressive in the naive study how fast viral loads dropped with raltegravir even though at week 48 the raltegravir and the efaverenz-based regimens came out the same. But, you know, up through the first almost 24 weeks there is really a striking difference in all the curves for raltegravir regardless of dose. So, maybe that is something that is exploitable in terms of a regimen that is not three drugs. I think we tend to think of three drugs as if it is written in stone but it is history.

DR. PAXTON: Dr. Grant?

DR. GRANT: Just to emphasize though that that study was done with raltegravir in the

combination of nukes, and it is not clear what is being proposed here but, you know, I think a small Phase 2 study makes sense. But we do not yet know how well raltegravir is going to stand up without nukes. All the data we saw was pretty much with nucleosides in the regimen. So, the data presented was clear that this is a drug that needs to be protected with other active drugs so, you know, I think a two-class/two-drug regimen makes sense, but on a small scale initially to first establish that the drug is active and doesn=t get defeated by resistance very quickly and then after that you can think about demonstrating efficacy over a longer term.

DR. FEINBERG: Sure. Yes, a staged approach makes sense.

DR. PAXTON: All right. Miss Swan?

MS. SWAN: If you are doing a two-drug/two-class regimen, definitely something that can really do the heavy lifting has to be included. It is nice to avoid some toxicities and use a class-sparing strategy. With the

three-drug/three-class the added toxicities can sometimes be hard to attribute. At least with two-drug/two-class that might be a little clearer. So, I think a pilot study is in order.

DR. PAXTON: Dr. Havens?

DR. HAVENS: Certainly I would be supportive to the FDA if they were faced with an atazanavir combination with no furtherB-atazanavir-raltegravir would look like a very promising two-drug combination to be compared to standard therapy, a triple for example.

DR. PAXTON: So, I am sort of hearing around the table that there is definite interest in the possibility of looking at raltegravir in a two-drug combination, however, there is a caution voiced that with the data that we have available we don=t know how it acts without a nucleoside present, so looking at it in more of a staged approach. Yes, Dr. Yarchoan?

DR. YARCHOAN: I would perhaps throw in that if any two-drug/two-class regimens are looked at that the patient should be followed for a

substantial amount of time. Twenty-four weeks just isn=t long enough to see the emergence of toxicities. The three drugs is in part historic but it is also because if resistance develops to any of those drugs you still have two to fall back on. When you get a couple of mutations with drug your are suddenly on thin ice and really dealing with monotherapy.

DR. PAXTON: Anything further on this? We have been talking about treatment-naive patients. Any more comments about that? Miss Swan?

MS. SWAN: I think if this is going to be looked at in combination with a protease inhibitor boosted would be the way to go just to give you a little extra protection against resistance.

DR. PAXTON: Then shall we talk about the (b) part of this question, which is asking essentially about nucleoside-sparing regimens or three-drug/three-class regiments in first treatment failures, not treatment-naive br first treatment failure patients? Dr. Andersen?

DR. ANDERSEN: Well, this might actually be

an avenue to answer some of the questions that were brought up earlier about the broad definition of treatment-experienced, that if it were a fairly standard regimen plus raltegravir versus an experimental plus raltegravir in first-line failure that might answer both questions at once.

DR. PAXTON: Any other comments? Dr. Feinberg?

DR. FEINBERG: Yes, I agree with Janet that it would answer those questions, but I think the practical thing is that it has proven to be hard to find patients at that magical moment. I think the other thing to consider is, you know, since most patients are started these days on a Q-day regimen and your first regimen failures would be failures of, you know, atazanavir-tenofovir-FTC or efavirenz-tenofovir-FTC then likely a first failure population is going to be a population that hasn=t gotten the habit of taking medication yet. So, I think you just have to take those kind of quirks into consideration in terms of study design.

DR. PAXTON: Miss Swan?

MS. SWAN: I think definitely second-line treatment strategies including raltegravir are an extremely important thing to investigate for the global significance as well as in this country and Europe.

DR. PAXTON: I totally agree. Does anyone else have a comment on this?

[No response]

Then I think we should move forward to the last one, what strategies would help increase study enrollment of women and minorities? Dr. Gordin?

DR. GORDIN: I was on this committee--I was trying to remember--either from >94 to >98 or >96 to 2000 and I can=t believe this question is still here, honestly. So, I don=t know what more anybody on this panel can say. I mean, go where the people are. Seriously, I am not sure what else anybody can say, other than trials need to be done where patients are who represent the epidemic. I don=t know.

DR. PAXTON: Miss Swan?

MS. SWAN: I think it is interesting that

we are being asked this question. I mean, it would be interesting to say to the sponsor what could you do differently or would you have done differently since the numbers were not good? I think I have a few very practical, very obvious tips but one place to really look is at state ATAP coordinators to get information about clinical trials because they may be in the position of telling people we can=t get you into this program and there are people that need access to drugs. It is not an ideal situation but it is a real-world thing that happens.

DR. PAXTON: Well, I have always had a question for the FDA. What do you actually require of the sponsors? I mean, can you say to them like in the pre-IND stages, you know, you must enroll X percent of women or of minorities? What do you customarily do with the sponsors?

DR. BIRNKRANT: We encourage them early on to enroll numbers that reflect the epidemic in this country if they are doing the trials in this country, or globally if they are going outside the U.S. It is unfortunate that we have to bring this

question up in 2007. As Dr. Gordin mentioned, we brought this up quite a bit in the past so we just thought we would go public with it once more so that other sponsors who may be in the audience could hear the suggestions from our experts on the advisory committee, and understand the great need to enroll women and minorities in these clinical trials.

DR. PAXTON: Dr. Hendrix?

DR. HENDRIX: Just to follow up on your comment, I think if you have regulatory authority to demand it up front before licensure and not make further pleads at the time an NDA is reviewed here publicly-I mean, if you had that, the industry would be able to figure it out. They solve every other problem; I am sure they would figure this one out. They are smarter than most of us here. Seriously. But only if they have to. So, until they really have to--

DR. BIRNKRANT: The regulatory authority that we have is basically at the IND stage where if the sponsor were to exclude women we could stop the

trial. But as far as having a certain number of women in the database, we can=t really, you know, put things on hold at that level or tell them that we refuse to file the application because there aren=t enough women in the application.

DR. HENDRIX: No, I understand your limitations but limitations can be changed. Not by anyone in the room.

DR. BIRNKRANT: That is true. But the other situation I think is that I think it is just important to continue to discuss this and come up with strategies. And, it was brought out about stratification. I mean, is that a reasonable approach to stratify for these groupings or not?

The other thing I would like to bring out is that, you know, sponsors have told us, well, either we go ahead with this database or you hold up an important drug while you wait for data in women. What would you like to do? So, could we hear a little bit of discussion about the stratification for these groupings?

DR. PAXTON: Dr. Grant, you brought that

up.

DR. GRANT: Yes, I think it is a good idea. I think that the FDA does have the authority to state that a protocol that enrolls a very small number of Blacks or a very small number of women is unsafe, and it is unsafe because it puts this advisory committee in a position where we are asked to approve an indication that extends well beyond the population that was studied. I mean, do we know that this drug is fully safe and effective in women? Well, I don=t think we do based on this data. The trends are all consistent but the data isn=t sufficient. So, I think the regulatory authorities should help out the drug development process by insisting on representative samples. I think in the end everyone benefits. We end up with better drugs that are better evaluated. This committee has more information to make decisions regarding how broad the indication should be. I would also submit that industry benefits because to the extent that clinical research is done in marginalized populations they will create treatment

advocates in those populations, and that is what is lacking right now. So, I think that everyone benefits.

I think the regulatory agencies need to nudge the companies, and one way to nudge them is to say if your protocol does not have stratified recruitment that assures at least 25 percent women and 50 percent Blacks we are going to regard this to be unsafe to proceed because you are going to push this development pathway into a pathway where decisions get made based on inadequate information. So, I think that you do have the authority to do that.

DR. PAXTON: Dr. Andersen and Miss Swan and Dr. McGowan and Dr. Feinberg.

DR. ANDERSEN: I think one thing is a clarification of terminology. Statisticians think of stratification as something that guides the randomization and things have to be balanced on it. Then, at the end of the day you have to then stratify your analysis. I think what we are in fact talking about is, as you said, a

representative sample. So, it means making sure that there is enough accrual but not a statistical stratification.

Another thing to bring up is agency oversight during accrual. Safety is being submitted. The question is whether accrual could be submitted so that there is some feedback on an ongoing basis. Some of the cooperative groups have, in fact, extended accrual for studies to pick up missing populations. That is one option that could be done on open studies.

DR. PAXTON: Miss Swan?

MS. SWAN: I am definitely in favor of targeting sufficient numbers of women and non-white males to pick up any signal of safety, efficacy and gather meaningful data. In the absence of current regulatory teeth to do that, I think labeling is another way to say, warning: this product has not been studied in enough women, African Americans, etc. to detect whether there is a difference in how well it works or if there are certain side effects or risks in a given population.

DR. PAXTON: Dr. McGowan, Dr. Hendrix and Dr. Grant.

DR. McGOWAN: I agree totally with the general principle that the study population should be representative of the U.S. epidemic. That is a given. But just not so much a note of caution as a practicality, the U.S. epidemic is moving and has moved into socioeconomically deprived communities with multiple social, economic and other challenges which will make them a challenging population to study in the context of an IND pivotal study. And, I don=t say that is an excuse not to do it, but based on my experience of working in economically deprived communities in sub-Saharan Africa, you have to put a significant amount of infrastructure at all levels to facilitate those type of studies and I think the same would be true if you are moving to populations in the U.S. I mean, the reason these studies can enroll and work is because they are bringing in essentially educated white males who will turn up and participate in the study as per protocol.

So, that is definitely not a reason not to do it, but I don=t think we can just take the box and say we would now like to have 50 percent of your population and expect the drug development process to continue at the rate we have seen because I don=t think it will happen. And, I don=t think the FDA will be happy with the adherence rates they will see without suitable infrastructure support and preparatory for these challenging populations.

DR. PAXTON: Dr. Grant?

DR. GRANT: I agree with Ian that investment will be required to create clinical trial sites in these populations. Where you get adherence you get high quality data. But those investments are well worth it. It is not just ticking a box. I think if the regulatory requirement were to become clear, the resources at that point would become available to create those clinical trial sites. And, I suspect that at the end of the day we would find that those sites were highly effective, highly efficient and the

adherence, in fact, was not only possible but in many cases better than in some of the populations that we have relied on in the past. When we have created new clinical trial sites, they often exceed the performance of existing sites. So, I would encourage us all to be adventurous and to make those investments that will be required to get more truly representative populations.

I have to disagree with my colleague. I don=t think that restrictive labeling is the answer here. I think at the end of the day we do need to foster treatment advocates in our marginalized populations, and what could be more discouraging than to read in the label that this drug, which looks so great in white men, hasn=t been really studied in your population? I am afraid that they would be discouraged and they would be afraid to use it.

DR. PAXTON: Dr. Gordin?

DR. GORDIN: Well, I also actually wanted to disagree with your point. I mean, if you look at the NIH networks, the CPCRA and now InSite and

the ACTG, there are extraordinary rates of women and minorities in the studies here in the United States, with very, very low loss to follow up in some of the studies, like SMART, in the range of one percent loss to follow up. So, yes, it is an investment of time and money but this is being done now by NIH and clearly can be cone by industry as well.

DR. McGOWAN: Just to answer, I am the co-PI of one of those networks so I am speaking from that experience. What I am trying to say is that there needs to be substantial infrastructure support and when that happens you can perform at the highest levels of clinical trials activity. But I think a company wanting to do a nine-month study may not have the desire to invest and, more importantly, have the permanent presence in those communities which will help you succeed.

DR. GORDIN: No, that I agree with totally and, again, it is a bit of a shock, having been off this committee for so long. At my site, I have not been doing many industry trials. I guess I would

have thought, incorrectly, that that infrastructure would have taken place over the last decade in sites similar to what NIH has used and others so that they do have trials that recruit high numbers of women and minorities and look at those sites as, you know, capable of doing multiple trials over years so, therefore, worth the investment of time and money.

DR. PAXTON: Jeff, you want to speak?

DR. MURRAY: I understand wanting a representative population, but I do want to say for this drug, at least for efficacy for the primary endpoint for the subgroup of females and Blacks, even though perhaps not representative of the population but I am not sure exactly for triple-class experienced population how far off we might have been, but I think for efficacy, efficacy has been proven and the 95 percent confidence intervals were on the other side of zero. So, even though it wasn=t representative the efficacy looks exactly the same. So, I think you had enough statistical power to show that this does work in

women and Blacks.

Now, as far as safety, there might be a safety issue in women or Blacks and you might need a greater sample size, but it is a little hard to predict from the outset what kind of sample size you would need to answer your study question in that case. It might be even greater than just taking kind of an arbitrary representative sample.

One thing that we talked about earlier, and maybe people want to comment on it is, aside from the pivotal study, besides having a regular kind of expanded access, having another kind of tier of kind of an expanded access program or a compassionate use protocol done at certain academic or designated centers where you can enroll a lot more patients to get more dedicated safety data. So, not as loose as expanded access; more dedicated safety data that would run while the Phase 3 trials were also finishing but could be more used for regulatory purposes. At least you could get safety data. Because at least in this instance, I think it is maybe more safety data that is lacking than

maybe efficacy because generally we do have a pretty good idea of what PK is in women and minorities.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: Just a quick comment, I think the issue is complex and the concern about clinical trial participation in some of the minority groups has been one of the issues because some things that have happened historically has been an issue of concern. But it is not impossible. Even in Bethesda, in our clinic in the Cancer Institute, I don=t have the numbers at hand but we have a fairly high enrollment of non-white minorities in our trials. So, if we can do it in Bethesda, it shouldn=t be that hard if people really put some effort into it.

DR. PAXTON: Dr. Feinberg and Miss Swan?

DR. FEINBERG: You know, I think the concept of targeting populations can work, does work. Federally funded groups, as has been mentioned, that work on that principle have gotten better and better participation by minorities and

by women. There is an ongoing study now that is the GRACE study that has a three to one female to male component as its overall accrual goal but then, within that, every site has to enroll three women before they can enroll a man, and it is also balanced for race and ethnicity, and that study has accrued extremely well.

So, I think it is possible if you put the energy behind it. Now, that is a post-marketing study of darunavir, not an IND, not a pivotal study. But, you know, it clearly can be done in that context and I don=t see why it couldn=t be done at the pivotal study level as well. You know, I think part of it is setting a study up that way and making it clear to investigators what their role is and then getting the right site representation.

DR. PAXTON: Miss Swan?

MS. SWAN: I am glad you mentioned the GRACE trial because I was thinking about that and I think, you know, with regard to Dr. McGowan=s comments, yes, you definitely need to develop an

infrastructure which is also crucial to good delivery of care and treatment. So, in every way it is a very good investment because it guaranties that products will be used in the best possible way to the extent that infrastructure and support can contribute to that. But sometimes the resources go into post-marketing commitments that could be pushed further into drug development. So, the GRACE trial is a good example but maybe that could have happened during the development. Maybe there is a way to do this. I think collecting data during an expanded access program is a very good idea and I am open to all ways that data can be collected.

I am not a statistician but I do wonder, 019 had 19 percent of women. I don=t know if that is enough to get all the information. Lastly, to the comment about restrictive labeling, I take your point and I think it is an excellent point but I also can tell you from my personal experience as an educator, people are always saying how many women were in those studies? So, it is a question that

comes up right away and needs to be addressed somehow, and sometimes the fact that women don=t have the information but need the drugs makes us into really determined advocates.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: Yes, if I could just put in a bit more here, I take the point that the data as shown do not show evidence of lack of efficacy in women. It would have been a shame at the end of the study to go, darn. Because these are some very wide confidence intervals, the rates could have been lower and still very important and, yet, have crossed the zero boundary.

The other issue is NIH studies are required to show explicit analyses of interactions, race treatment with outcome, gender treatment with outcome. The numbers here aren=t sufficient to do that with enough power to detect anything going on, if there were suspicion of something going on. So, I think the issue is to preplan because, again, it would be a shame at the end of a study, an important study, to have something s inexplicable.

DR. PAXTON: All right, I think we have heard a lot and I am always happy to here this as both a woman and a minority. I think we have heard a lot about up front making it clear about expectations. Maybe if the FDA could have a little more teeth in its regulations about requiring that and, of course, the recognition that it is going to take a lot of infrastructure to get this but it is worth it in the long run and actually has to be done as a safety issue.

Unless there are any more comments on this particular question, I think we can consider that we have answered everything. Do you have any other ones that you would like to pose to us?

DR. BIRNKRANT: No.

DR. PAXTON: Great. Cicely, do you have any final things you would like to say to the group?

DR. REESE: No.

DR. PAXTON: Well, then I would like to thank you all for having attended this meeting, particularly the committee members and those who

participated in the open public hearing. Thank you very much.

[Whereupon, at 3:20 p.m., the proceedings were adjourned.]

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