load and a raised CD4 count. You would hope that that would outweigh the risk benefits of West Nile virus in this heavily treatment-experienced population.

DR. PAXTON: Dr. Gibert?

DR. GIBERT: I have two questions and then maybe a comment. With respect to the CPK which Dr. Proestel presented, the CPK data on page 16 of his handout, do you think those patients were receiving T-20, who had elevated CPK who also seemed to have a higher rate of elevation in CPK on maraviroc? Or, do you think this might be some wort of mitochondrial toxicity that is related to maraviroc?

DR. DUNNE: So, the question is really do--

DR. GIBERT: I guess the people with elevated CPKs, were they also receiving T-20, which I think can elevate your CPK simply from the injections?

DR. DUNNE: Sure, Dr. Felstead will talk to CPK.

DR. FELSTEAD: I think in terms of the

specifics, we need to run the analysis for you and we think we can let you know later on today. We don't have a slide for that now.

DR. GIBERT: Is there any thought to consider this as possible mitochondrial toxicity from the maraviroc?

DR. FELSTEAD: Well, when we examined the CPK data we showed that at baseline over 25 percent of subjects had elevated CPK, and the difference was slightly balanced in the maraviroc groups with 28 percent and a little bit lower than that in the placebo group.

DR. GIBERT: But I think a number of people were already on T20 at the time of study entry?

DR. FELSTEAD: I am sorry?

DR. GIBERT: Some people had T20 in their background therapy prior to enrollment or in their OBT.

DR. FELSTEAD: Yes, they would have done but I don't have that analysis.

DR. GIBERT: And with respect to the increased incidence of herpes simplex virus, do you

think any of this constituted an immune reconstitution or represents immune reconstitution?

DR. FELSTEAD: Well, I would be speculating but we did do an analysis looking at the first 8 weeks of dosing of maraviroc to try and overcome this rapid drop-off in placebo control. So, if you compare the first 8 weeks of therapy only, then there were 2 events on placebo, 7 events on maraviroc QD and 12 events on maraviroc BID. But that is simply an analysis of the data, not an interpretation of it.

DR. GILBERT: And I just have one other question, I am sorry. Do you have any thought of using ritonavir alone to boost maraviroc? In other words, to look at the effect of maraviroc on ritonavir and sort of take the other protease inhibitors out of the picture?

DR. DUNNE: No, because I think, as Dr. Mayer showed, the 300 mg BID dose appears to perform very well in the absence of ritonavir.

DR. GILBERT: So, on page 149 you are suggesting I think that you really are seeking

approval of the twice daily dose. Is that right?

DR. DUNNE: Yes, that is correct.

DR. GILBERT: This is the last thing I will say, there is also this question of CNS penetration. I think it is about 10 percent according to what I read. I think as we are treating more elderly patients, like myself I suppose, is there any concern about neurological sort of problems in people who are receiving maraviroc and other drugs which really don't get very adequate CNS penetration, or also the risk of PML, as well as just sort of HIV encephalopathy or Alzheimer's?

DR. DUNNE: Can I just reflect the question back to you? Are you concerned about maraviroc not getting across the blood-brain barrier or getting across?

DR. GILBERT: I think it said 10 percent in what I read in your materials even if it doesn't get across, so is it increasing the risk of, like, HIV encephalopathy or things such as PML or Alzheimer's as we treat many more older patients

with HIV?

DR. DUNNE: We did ask if any CNS samples were collected during the Phase 2b/3 program that we could actually have some sent to Pfizer for assay. Unfortunately, only one patient sample arrived and that was a placebo patient. So, I can't give you any human data so we still have the estimate of 10 percent from the rat data.

In terms of risk, yes, we believe that limited penetration would be PgP driven and in the presence of a PgP inhibitor, such as most of the protease inhibitors, the 10 percent extrapolation from rat to human may be an even greater extrapolation but we don't have data.

In terms of risk, then I think again we fall back into the risk management plan of how we examine rare events across the population over time with far more data. I don't believe we had very many patients in the program that were over the age of 65.

DR. PAXTON: I am going to be a strict taskmaster so I am going to allow, depending on the

length of the question, one or two more people, but I want to remind you that after lunch we are going to come back and we will have opportunities to ask more questions. So, Dr. Weiss Smith, you were next.

DR. WEISS SMITH: Just two quick questions, I hope, to the sponsor. On slide 145, the risk management studies that are proposed, I wanted to know what exactly is a safety registry that is being proposed. How is it different from postmarketing surveillance?

DR. DUNNE: Sure, Dr. Felstead can speak to that directly.

DR. FELSTEAD: So, a safety registry is where information is collected. The patient comes to the clinic and it is a normal clinic visit. They have to give consent but a questionnaire is filled out and provided to the sponsor or to a third party in terms of collecting straightforward information that is regularly collected on HIV patients at each of their clinic visits. Our goal is to have 2,500 patients at least in this

registry, collecting detailed data on key important events. With about 4,500 patient-years of follow-up we believe we could detect doubling of rare events. It is a questionnaire and, of course, it relies on maraviroc being available on the market.

DR. WEISS SMITH: So, it is more of a cohort approach then?

DR. FELSTEAD: Yes.

DR. WEISS SMITH: The other question is given the unique population, how do you propose to interpret the safety data, particularly the more common adverse events, without a comparator group?

DR. FELSTEAD: Well, there are several ways of addressing that. The first is that we have a collaboration with the Euro SIDA group and what they have done is identified a group of patients that met our protocol entry criteria during the period of recruitment of the protocol. This cohort has been identified and from that they will estimate the expected event rates when adjusted for a particular characteristics of our clinical

trials. So, we are trying to make an ever-diminishing placebo group and to have that as the control group for our treatment-experienced studies.

In addition, of course, we do have the treatment-naive study ongoing which we hope will be quite informative in terms of trying to tease out any maraviroc signature adverse events.

DR. WEISS SMITH: I guess I am more thinking about once it is on the market, what is the comparator to the people who will be prescribed the drug?

DR. FELSTEAD: Yes. So, the comparator would be the people who are not prescribed the drug so it would be converse. I accept the limitations of registries in terms of that so, yes, it does not have a control group being brought into the registry.

DR. PAXTON: Well, in the interest of keeping to time, I am going to go ahead and defer. We have Drs. Dee, Havens and Andersen who have indicated that they want to ask some questions.

So, we will hold you until after we get back from lunch.

We have an hour for lunch. I don't know if you have suggestions about where everyone should go. I presume we will all end up in the lobby. We will see you back here at 1:30.

[Whereupon, at 12:30 p.m., the proceedings were recessed for lunch, to reconvene at 1:30 p.m.]

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

DR. PAXTON: We are going to finish up few questions from the session before lunch. Then, after that I am going to call the committee's attention to the list of questions that were given to us in our packets. I think we are going to want to structure some of our discussion around these questions so we can answer some specific questions that the FDA has for us. Dr. Dee, Dr. Havens, Dr. Andersen and Dr. Alexander have some questions from before the lunch period so we are going.

I am sorry. I have just been reminded to make the announcement that on your agenda you see that this is supposed to be the open public hearing part but we have no speakers schedules for that. So, that is why we are going right into the discussion session. All right, Dr. Dee, you are up.

MS. DEE: You know, my blood pressure has since calmed down and really my question was a comment about the idea that there were not enough women in this study. Everybody was talking about

Blacks and Hispanics and people with HBV and HCV. So, I am happy to just make that comment and save my questions for the question part of that in the agenda.

DR. PAXTON: All right, then Dr. Havens?

DR. HAVENS: Thank you very much. I am going to try to do a little better with the kinetics question that I feel like I failed with before. So, on the sponsor's slide number 62 they suggest that they agree with the FDA's suggestion that there is a target C_{min} that is associated with outcome. The question would be in the 300 mg BID group, which was unboosted drug, what percentage of patients in that group meets their target C_{min} of 50, and in the 150 mg BID group what meets the target C_{min} of 50? Does sponsor have data to show on that?

DR. DUNNE: We are checking. Yes, Dr. McFadyen will try to answer that question for you.

DR. HAVENS: Or we could go to the FDA slide if you would prefer.

DR. McFADYEN: Yes, I think it is on the

FDA slide.

DR. HAVENS: Okay, so maybe we could go to that FDA slide.

DR. JADHAV: Which slide are you referring to? Is this the slide?

DR. HAVENS: It was on page 5. Yes, it is the next slide, what are the important predictors?

[Slide]

So, this 300 mg BID without a PI, so that is unboosted. First of all, that is a pretty small group, 88 in the unboosted group. If we choose what sounds like the sponsor's target C_{min} of 50, this would suggest that 66 percent did not make it to the target C_{min} with unboosted drug. Is that an accurate understanding of what this table is suggested to show?

DR. McFAYDEN: That table does show you what proportion of patients reached the specific targets, but I think one needs to emphasize that there are a number of other factors which predict efficacy as well as the C_{min}, and I think that was made in the FDA's presentation as well. So, a

target is fine but you need to take the CD4, the OSS, etc. into account at the same time, and one doesn't want to treat a target concentration. One needs to treat the patient in entirety. But it is absolutely correct that a much smaller proportion meets either the FDA's target of 75 or our target.

DR. HAVENS: Well, I don't care, let's just choose one target to talk about because here, with the boosted drug you are using a lower dose but boosting actually gets you to the same target over 80 percent of the time. Right?

DR. McFAYDEN: That is what when you are talking about--

DR. HAVENS: So, unboosted drug misses the target almost two-thirds and boosted drug gets you there really, really well. Right, it is always going to be better if your CD4 is higher and your virus load is lower, and if you have more good drugs in your optimized background regimen. That is why these studies are tricky to analyze, and why you need to be careful to look at this kind of drug specific information so that you can try to

separate the drug specific information from the information that is wrapped up in patient factors and other drug factors, like what is in your OBT. But I just want to make sure we agree on this.

DR. McFAYDEN: Yes, we agree.

DR. HAVENS: Thank you. Then, do you have the slide that shows what this boosting was? Because one of the questions that comes up is, well, why don't you just boost with ritonavir and it is a little bit trickier than that. Could you show us that slide that we have in our handout? It is figure 1 by C_{max} or figure 2 by AUC.

[Slide]

DR. JADHAV: Is that the slide you are talking about?

DR. HAVENS: Yes, I think that is it. This is the issue. Here, what we seeB-it is hard for me to seeB-this is what is nominally called the 150 mg group and this is nominally called the 300 mg group, but really this is unboosted and this is boosted. Now, the problem is that these are all boosted by a variety of different combinations and

there are different amounts of boosting. So, what you are trying to do is get up into some sort of range where it is going to work. The problem is depending on what you boost with-Bhere is saquinavir/ritonavir, the peak there gets high so if we are not looking at the signal by trough or specifically what it is boosted by it makes me worry for QTc, for example, which was not in the range that we saw, or other potentially dose-related toxicities if, depending what you boost with, gets pretty high.

So, it is different than other kind of boost with ritonavir studies and it is pretty complex for me. I am still just trying to understand. Is there a way that we could do this analysis that would help us to see these signals, here? You know, lopinavir is a little lower but still boosts quite well. Over here, this is tipranavir or tenofovir. That was the 300 BID group so those are much lower and likely to be safer, although it is a much smaller group, right? This is about 88 over here and 300 over here,

depending on how you did the analysis. So, is there a way to capture those kinds of patients with the higher trough in these boosted groups? FDA or sponsor, I don't care, take it.

DR. DUNNE: Maybe I can just clarify that. You want to look at an outcome variable around boosting versus non-boosting. We had a suggestion before the break about efficacy, with a boosted PI or not, being pretty much the same within the 2-5 percentage points difference in efficacy that we are seeing because basically both QD and BID are approaching the plateau of effect. I think we showed that earlier, and I think what you are asking is, is there something happening, some other outcome variable associated with higher maraviroc serum levels, for example in the boosted group, which is either good and/or bad, and do we need to explain more of that to you.

DR. HAVENS: Well, yes, that is maybe a good way to say it because the analyses we have seen mix these problems together with BID versus QD, boosted versus unboosted, and lots of different

ways of doing it.

DR. DUNNE: Okay, so just to break it back down, I think with regard to efficacy we can show that slide one more time. You remember from before the break the Pis--

DR. HAVENS: No, that wasn't the question. The question is on the prior FDA slide showing that a very small percentage of patients treated with unboosted maraviroc reach a target that the company suggests is important for activity of 50 ng/mL.

DR. DUNNE: Yes, and again, just to reiterate what the analyses showed is that while going for a higher target you move your efficacy rates, which is the less than 400 endpoint we are looking for, by about 2-5 percent. That was the difference in efficacy that comes about because of the different exposures that we were getting, depending on the ng/mL level that is reached with the dosage regimen on a population basis.

DR. HAVENS: But that is mixed unboosted and boosted, and those populations are so

dramatically different that that is not a proper analysis, from my perspective.

DR. DUNNE: I think--

DR. HAVENS: No?

DR. DUNNE: I think if we show the slide again perhaps--

DR. HAVENS: Well, no I know the slide, once a day, twice a day--

DR. DUNNE: And one was boosted and one was not boosted so we didn't mix the boosting in that slide. There was a boost and there was a no-boost. So, maybe we can help with some efficacy statements around --

DR. HAVENS: No, I understand--

DR. DUNNE: I am sorry, safety.

DR. HAVENS: You know, it is 24 weeks and I think whether or not the trough is important may show up later in your studies. A lower dose once a day didn't work in naive patients. You told us about those data.

DR. DUNNE: Yes.

DR. HAVENS: So, a trough probably is

important and the point has been made. Thank you.

DR. DUNNE: Okay.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: Yes, I am going to perseverate a bit on the issue of race again because my understanding is that the application does not have limits on the population; it is just a broad application. The data that we have seen, and this includes the re-summary by the FDA that is focusing on, for example, the endpoints Dr. Kuritzkes brought up that, you know, in this population we can begin to talk about really substantially getting people to below detectable. And, what we have in the FDA summary, again table 5, shows essentially identical response rates, black versus white populations on placebo, and not that much difference between placebo and the maraviroc arms BID or QD.

So, yes, you know, we were shown some univariate adjustment for how many active drugs there were. What I would like to recommend is that a formal analysis of interaction be done that

adjusts for covariates that are important. Potentially, if you have enough subjects, look at the recommended dose not just, you know, everything. And, consider what more information is needed. It was brought up that the plan is for there to be additional studies, to use the EuroSIDA data as the comparator. There are not a lot of black subjects in the EuroSIDA data so it is to preplan how these things are going to be done over the future and really have an identified control population or comparator population and move forward.

DR. PAXTON: All right, the next person is Dr. Alexander.

DR. ALEXANDER: Thank you. I have a couple of questions. Just for practicality purposes, is there an assay for level detection of the drug available commercially?

DR. DUNNE: No, there is no serum level assay available.

DR. ALEXANDER: So, we wouldn't be able to recommend serum level assays even if we wanted to.

DR. JADHAV: Sure, it is agreed upon that right now there is no bedside, let's say, assay that is available readily. However, there are other drugs that are used, on similar lines, and similar assays have been used for immunosuppression for surgery patients. But it is acknowledged that for maraviroc there is no readily available assay at this moment.

DR. ALEXANDER: Next question, looking at the averse events and the increased incidence of HSV infections, have you given any thought as to a specific theory about the mechanism behind such perhaps reactivation of HSV, or is there any theory behind the mechanism for it?

DR. DUNNE: I can try to answer that. I think we can imagine that there could be different ways that use of maraviroc would bring out HSV infection. It would really be speculating at this point. Again, we just tried to present the data as we saw them in the studies and then, you know, from there we can just discuss that freely. So, it was mentioned it is possible there is an immune

reconstitution syndrome which could be showing symptomatically some of these underlying infections which are not seen otherwise. But we don't have data to say there is or isn't that particular syndrome happening at this point. So, we don't really have much more to say about the reason why there might be HSV increases.

DR. ALEXANDER: My last question has to do with low concentrations of the drug and the potential that that is what is driving some of the mutagenesis and the resistance. I think I heard you mention that the patients who actually had developed some of the changes and the genotypic resistance mutations were actually those who had lower level--

DR. NAEGER: Yes, the 5 patients who had the lower plateaus and maximum percentage inhibition had low C_{min} values. I have a slide I can show you.

[Slide]

This shows the 5 patients and their C_{min} values and also the baseline susceptibility score.

The 1 patient that was placebo actually developed the lower plateaus on open-label maraviroc so we didn't have a C_{min} value for them because they were originally in the placebo group.

DR. PAXTON: Dr. Hendrix?

DR. HENDRIX: No.

DR. PAXTON: We have Dr. Gibert and Dr. Grant.

DR. GIBERT: Going back to the question that Dr. Havens raised, when you are talking about boosted, most of the protease inhibitors that you show in the tables actually don't appear to be boosted, except for the Kaletra and saquinavir/ritonavir. So, in reality most of these drugs are prescribed to treatment-experienced people with concomitant ritonavir. And, when you add ritonavir to these drugs when you are trying to optimize their sort of background therapy, you boost the level of the maraviroc and I don't know what the therapeutic window is but I think you may go above the therapeutic window, as well as being below it. I don't know if you have any information

as to when the concentration is below the minimum concentration which you appear to be seeking, of 75, does that increase the risk of tropism shift as well? I mean, is it mechanism of resistance, just sort of typical phenotypic and genotypic resistance? Or, is it actually tropism shift at that juncture? Is there any way to clarify that?

I think what Dr. Havens is driving at is that we have a pretty narrow-Bwe may have a much narrower therapeutic window. When the drug gets too high you may have more postural hypotension or more QTc prolongation. In the documents which you have submitted you talk about the occurrence of postural hypotension with higher doses of the drug, and I sense there is a discomfort from the panel about the sort of correct level and correct dosing of the drug.

The question is do you have any data on using boosted protease inhibitors other than Kaletra and saquinavir in terms of drug levels? Then, the other question would be are you concerned about the upper limit of the drug level? The third

question would be when the drug is sub-therapeutic, given the fact that there is so much lack of adherence and that is why many of these patients got to where they are anyway, does that drive resistance which is based on genotypic and phenotypic change, or is it tropism shift?

DR. DUNNE: We will take the first question first. Dr. Mayer, do you want to start off now?

DR. MAYER: No.

DR. DUNNE: Okay, Dr. Felstead will talk about the safety related to the different protease inhibitors.

DR. FELSTEAD: We did a number of drug-drug interaction studiesBsaquinavir, Kaletra; we have completed derunavir as well. During the Phase 2b/3 program we allowed the whole range of approved protease inhibitors and we collected sparse PK samples, which is what we are talking about. So, if I could show slide S-50.

[Slide]

The goal of our whole program in terms of dose adjustment was to manage the C_{max} because of

the temporal association of postural hypotension. What I am showing here on this slide is, in the brown, a curve of all the 300 mg BID data we have from enriched sampling in Phase 1 and Phase 2a, and the concentration is on the You axis and the time after dose on the X axis. All the other dots are those sparse samples, observed samples from the entire Phase 2b/3 program. The ones in black are the ones that haveB-I have been given a laser pointer. It may not reach this far. Yes, it does; not it doesn't. Maybe I am just not pointing it accurately enough. I will go to the podium.

Yes, it does work. So, the brown or the orange gives the entire range of concentrations that we studied at the 300 mg unboosted dose. This is enriched sampling from Phase 1 and 2a studies. All the other dots are all the observed concentrations for the Phase 2b/3 program. What I have highlighted here in blue are the drugs that we expected to be a strong inhibitor, such as saquinavir/ritonavir, and then probably the greatest inhibitors are actually dual boosted PIs

that we used within the program.

Recall that the goal was to manage C_{max}, not manage AUC, when we set off. What we can see here I think, with the exception of one outlier, all the observed concentrations that we collected during Phase 2b/3 were within our target range. I think this is why we see very little postural hypotensionB-in fact, we see no symptomatic postural hypotension and we find if very difficult to find any measured in the clinic.

Also, with respect to QTc, the study that I described this morning had a range of maraviroc concentrations that ran to 2,360 ng and the maximum value we have observed in Phase 2b/3 is 2,470 ng. So, it is within 100 ng/mL.

DR. JADHAV: If I can use the same slide, the patients that we are talking about here that might have potentially lower concentrations and could potentially get dose adjustments are the ones who are in the lower range of this curve. So, even if the dose adjustment is done, the peak concentrations as well as the trough will probably

not exceed the concentrations that are already achieved in the Phase 2b/3 trial.

The second point, I did not understand the question about boosting versus unboosting from you, but most of the patients in the Phase 2b/3 program, when they got PI, it was boosted.

DR. GILBERT: What is shown on the table just lists the drugs without concomitant ritonavir, if I read that correctly.

DR. JADHAV: Yes, that is the Phase 1 program so some of the drugs were given with ritonavir and some drugs were not.

DR. PAXTON: Dr. Grant and Dr. Yarchoan.

DR. GRANT: I had some additional questions about the hemodynamic effects of maraviroc. In the slide presented by the sponsor we see that there is some postural hypotension at the 600 mg dose but not at the 300 mg dose. It says in the box here that there were no adverse effects on cardiac index. The briefing materials describe a non-invasive hemodynamic study of 900 mg, indicating that there were increases in cardiac

index associated with reduction in systemic vascular resistance. It does not say how many people were studied or what proportion of them had hemodynamic effects. Yes, I guess it does say that there are 3/16 in that small study that had postural hypotension at the 900 mg dose.

So, the short question is do you have any non-invasive or invasive hemodynamic data at the unit dose that you are requesting for an indication, 300 mg? Do you have any such data? So, that is the first question. I would love to know more of the details of the non-invasive hemodynamic studies.

DR. DUNNE: Dr. Felstead will address that question.

DR. FELSTEAD: We did a study to particularly examine the effect at super-therapeutic dose. We did not see any signal at all at 300 mg, as I showed to you, so I saw little purpose in conducting a study at the 300 mg dose at the time. We did a study, I think it was in 16 healthy volunteers and we used GTN as a

positive control. If we can just project slide S-8?

[Slide]

I think these are the summary results. It was really a comparison of single dose, 900 mg of maraviroc, on hemodynamic comparators versus active comparator with blood pressure, heart rate and impedance cardiography. We also measured QTcF in the study as well.

[Slide]

Slide S-10 gives a range of the cardiac index seen. Remember, this is supine. There is percent change from baseline on the You axis here, time post dose, and this is cardiac index. This is the 900 mg maraviroc dose and this is placebo at the same time course. Here, and I am finding it difficult to read from the side, we have GTN which was the positive control which we ran just to ensure we had assay validity. So, these were small changes.

However, this was supine cardiac index. You are quite right that we did see I think 3

subjects in the study that actually did get postural hypotension when we completed these measurements and they stood up and walked around.

DR. GRANT: When you say there is no signal for hemodynamic effects at 300 mg unit dose, are you referring to the postural hypotension data from Phase 1/2a?

DR. FELSTEAD: Yes, I am.

DR. GRANT: Well, that is a relatively insensitive index of hemodynamic change. Remember that postural hypotension really is a state of decompensated hemodynamic circulation where cardiac output has not been able to increase compensatory with decrease in systemic vascular resistance. So, given that you are seeing a signal at 600 mg, I think it would be appropriate to look, using more sensitive measures for hemodynamic effects, at one step lower dose, especially since that is the dose that you are requesting an indication for.

DR. FELSTEAD: I think it would be best if I just take that back and we just discuss that.

DR. HENDRIX: Along the same vein, you

know, I think it is striking that your ischemic adverse events, all-causality, are appearing primarily in the active arm and not in the placebo. One wonders if, in fact, you are unmasking patients with asymptomatic ischemic heart disease using what amounts to a dobutamine challenge test with decreased systemic vascular resistance, increased heart rate which is going to unmask.

Now, one way to look at that would be to look at those who roll over from the placebo arm onto the active arm at the end of one of these studies. If that hypothesis makes any sense you might see that in those who roll over you would start to pick up some ischemic heart disease that you didn't get in the placebo arm. The question is do you have data on those who roll over from placebo in the active arm?

DR. FELSTEAD: No. Unfortunately, it is a very short time frame. We only have 40 patient-years exposure so far in the open-label study group.

DR. HENDRIX: Finally, in terms of

management of elevated lipids, do you have drug-drug interaction data on lipid-lowering agents in the context of the drug?

DR. FELSTEAD: We don't have drug-drug interaction data in terms of exposure. We have done an analysis of CPK with concomitant use of statins and we do not see a signal.

DR. PAXTON: Dr. Yarchoan, I think you were next.

DR. YARCHOAN: I have two questions, one about influenza and one about the tropism of the HIV. With regard to follow-up, chemokines can potentially affect influenza infection either by helping in immune response or by being part of the problem in exacerbated immune response, as has been proposed with some of the H5 follow-up, and I was intrigued that there is somewhat increased influenza reported.

First, are these actual cases of documented influenza or are these just influenza type illnesses? If they are follow-up, do you have any data at all on whether the increases might be

related to either poor control of the infection or exacerbated symptoms due to an exacerbated sort of dysfunctional immune response?

DR. DUNNE: So, these reported symptoms are not diagnosed microbiologically or serologically. They are basically the investigator saying my patient had an influenza-like syndrome and then reporting that on the case report form. Sorry, what was the second part of the question?

DR. YARCHOAN: Well, just with regard to that, why that might be and, as a follow-up, how you might want to look for that as the strains of the follow-up change?

DR. DUNNE: So, this is similar to the question that was asked before about the mechanism. Of course, we would just be speculating on that so far. We wanted to make sure we got the data out for everybody to look at and we will have good conversations about the "why" question as we go on. So, as I said, we are committed to continuing to follow patients on maraviroc. Those will be described after launch with the risk management

plan. We might be able to refine the signal one way or another when we have a bigger database. I think for now though it is just an observation that we just need to follow.

DR. YARCHOAN: The second one relates to the tropism of the virus. You seem to document some cases that have converted to an R4- or dual-tropic strain, and then when your drug is stopped revert back to an R5-tropic strain. It is actually an interesting experiment and suggests that in some patients there is pressure to go back to R5. I was wondering if you all had any speculations as to what the mechanism of this might be and any implications.

DR. DUNNE: Sure. Yes, it is a bit of a speculation. There are some facts that we will put out there as well and Dr. Westby I think can best address that question.

DR. WESTBY: I think the facts are that in the patient population from the 20 patients that we looked at in great detail, we think that what is happening is that the selected suppression by

maraviroc of the CCR5-tropic virus is actually unmasking the dual- and mixed-tropic virus. Once we take that selective pressure away by stopping maraviroc treatment, then the CCR5-tropic virus that was there grows back, very much in a similar way in which fitness mutation might be manifest once the patient goes on a therapy and then when they go off the virus returns to a wild type.

DR. PAXTON: Dr. Havens and Dr. McGowan.

DR. HAVENS: Just a question for the sponsor. On slide 148 it was suggested that the dose recommendation for 300 mg BID would be when given with tipranavir, ritonavir, NRTIs and enfurvitide and then nevirapine showed up in that group, which was a surprise to me given the prior data on efavirenz. Did I misunderstand?

DR. DUNNE: Yes. No, that is a reasonable question and Dr. Felstead can answer that.

DR. HAVENS: Thank you.

DR. FELSTEAD: Well, it says in the briefing document that 600 mg would be recommended. This was a consequence of an interim analysis of

the PK/PRODUCT data on the first 500 patients who came into the study and we suspected, both from literature and from those initial patients and we compiled some of the rest of the population who were not receiving nevirapine, that nevirapine was going to turn out to be an inducer of maraviroc metabolism. But when we saw the final 1,000 patient database, together with the single-dose study that we conducted back before we initiated the program, we rethought our position and we believe that nevirapine has no meaningful impact on maraviroc's concentrations. So, we are recommending 300 mg twice a day. So, I apologize to the committee. It was when we had to get the briefing document out at the end of March. Our position has changed since then.

DR. PAXTON: Dr. McGowan?

DR. McGOWAN: I was wondering if we could just go back to some immunology because we haven't really emphasized that so far. I mean, as pointed out by you at the beginning, this is a new class of drug. You are actually antagonizing HIV

co-receptor pretty effectively. And, your briefing document you gave some background on immunological assays conducted in animals of various species, but there was a significant paucity of information from humans. I presume that is because you have not done it. But it would be interesting to know what changes in immune responses occur. Particularly I am thinking of things like T-cell phenotype and particularly co-receptor to phenotype in subjects, be they healthy controls or patients with HIV over, you know, prolonged exposure to the drug. Do you have any data in humans, or do you plan to acquire any data?

DR. DUNNE: It is a good question. Yes, we didn't present that here today but we do have some information on immune effects in humans when dosed with maraviroc. Dr. Mayer will talk to that.

DR. MAYER: We don't have any data from Phase 3, but a study that we conducted was published at Croye earlier this year of 28 days of dosing from Phase 1 and 2a studies, looking at T-cell subsets, CD38 positive and Cd4 and CD8 cells

and K-cells and B-cells, and in those subjects and patients there was no consistent effect on immune markers.

DR. McGOWAN: Just to be a little more specific, you didn't mention C-cell either or whether receptor density is increased on T-cells.

DR. MAYER: We have no data on that.

DR. PAXTON: Dr. Rodriguez-Torres?

DR. RODRIGUEZ-TORRES: Looking at the dossier, I noticed in table 68 a series of adverse events in a patient that was labeled as hepatic cirrhosis. As hepatic cirrhosis is a pathological diagnosis, I imagine that this was partly decompensation, especially when it says that the patient was ruled out to have portal vein thrombosis. You reported PK studies done in mild and moderate liver dysfunction. I assume you are meaning child A and child B?

DR. FELSTEAD: Yes.

DR. RODRIGUEZ-TORRES: You haven't done studies in severe dysfunction?

DR. FELSTEAD: No, we have not.

DR. RODRIGUEZ-TORRES: That is important because if the drug goes out there it is going to be used in every kind of patient.

The last question I wanted to ask is to Mr. Jadhav from FDA. You presented a slide at the end that, in the view of all the discussion about exposure, is rather confusing to me, where you saidB-if approved eventually, it is going to be the first individualized they for HIV and you presented a slide on practical aspects of individualized dosing of the drug. Taking into consideration, for me, strange difficulties with exposure and the effect of the sensitivity to the background therapy and the tropism and the virologic change, in addition to exposure, how are the treaters going to deal with this if you don't have a way to measure this drug in the blood? If there is any doubt, how are you going to do this? You are not just going to be treating the liver complications; you are going to be treating the patients. So, please explain that to me.

DR. JADHAV: Sure. The comment that was

made about practical aspects, I was actually putting everything together, the whole picture of what it would take to treat every patient in the clinic. What we realize is that right now by using the simplest strategyB-I mean, there could be several strategies, but the simplest strategy of doubling the dose in concentrations less than 75 ng/mL increases the response rate by 2 percent. Now, what is up for discussion is what is the meaning of those 2 percent in reality.

But we also have to acknowledge that since we are using dose doubling, our safety data on high doses is limited. But, also, since we have established different relationships with factors such as CD4 or baseline viral load it is possible sometimes that viral load could be so high that the concentrations are such of maravirocB-and specifically when I said practical aspects I am focusing on maraviroc-Bthat maraviroc assays might not help. You might have to resort to some other antiretroviral agents in addition to maraviroc where you could use a similar strategy. So, there

are a lot of factors that would lead to define the success and, surely, ideally if there is a way that we could measure all the patient-related factors that contribute to success we could think about, you know, personalizing the medicine. But we used the simplest strategy that will kind of be practical to implement, rather than giving complex recommendations in labeling.

DR. RODRIGUEZ-TORRES: No, I understand your thought. It is very clear. My question is, well, then you need to have how to measure this drug in blood for the treater to assay safety and make more intelligent decisions.

DR. JADHAV: Sure. I think as a community, that is a challenge to us.

Discussion/Questions

DR. PAXTON: Well, this has been great. I think we are going to continue to ask and answer questions here but I would like to sort of direct further discussion and question answering around sort of the questions that have been posed because, as you know, we are never asked to just give a

simple up or down vote. You always ask for more recommendations from us. So, I believe that there is a slide up about this but you also have in front of you the specific things that we have been asked by the FDA to address.

Of course, number one is that they simply want to know do we support accelerated approval. But then there is a lot that has been asked about what additional data we might want to see. Already I am hearing things coming out of this discussion. I would like to certainly focus that a little bit more.

The second question is about discussing safety concern issues with respect to maraviroc, and to provide recommendations for possible product labeling, postmarketing studies and postmarketing risk management strategies.

The third is about do the data support the applicant's proposed dosing and to consider the recommended dose in light of the exposure-response modeling. Of course, with the whole boosting discussion that we have had I think that is

certainly on a lot of people's minds here.

Then there is the Monogram Trofile assay that I had asked about before. They want us to recommend how this assay might be used for the management of subjects here. I think that we are actually already expanding the discussion here. We just talked about the role of blood levels of maraviroc; how would we use that given the fact that it is really not available to us. It is kind of a dilemma from my standpoint.

The final thing is please discuss the impact of the availability of maraviroc on the design of future Phase 3 trials for new antiretroviral agents. I think this was posed as a bonus question to us, but I certainly find that an interesting thing that we should be looking at and we should be providing recommendations about how these trials should be designed accordingly.

So, what I want to do is to see if we can kind of structure the rest of our discussion around these basic questions here. So, I would propose, you know, taking them in order. We have started to

touch on some of the additional data that we would like to see, and if I can summarize the things that I have been hearing, and you can expand on that, clearly, one of the first things that came out was race, you know, the thing about the effect on African Americans, the lack of data on Latinos. We didn't mention about other groups like Asian Americans and the like.

And, that was my second one. The second one that came up was gender. You know, the effects on women.

A third thing that came up was more about people who are hepatitis-infected because that is going to be a large part of our patient population that would be affected by this.

We started talking about do we need to know more about hemodynamic effects and how would that be best assessed.

So, I would like to see if there are other things we would like to add to that list that I pulled out from what I heard. Yes, Dr. Dee?

MS. DEE: As far as the safety concerns, I

think we should also add immune-related signals to that, the liver function, cardiovascular issues. I mean, even though the numbers seem to be small and there was an effort to try to explain them away, I feel like I am not satisfied that nothing is happening there. So, I am very glad that we are doing this five-year long-term study to look at all this stuff but I think that we have to at least mention those things regarding safety.

DR. PAXTON: All right. Did you want to expand on that, like any particular designs?

MS. DEE: In other words, I mean I have an idea but I think they are going to look at some of that in that long-term study, but I think that, you know, it would behoove us to say some of the things that they should be looking for or not looking for. I mean, the hemodynamic stuff was not mentioned by the sponsor as one of the things they were going to be looking for. Some of the things were mentioned. I mean, I think they didn't specifically-I mean, liver probably would be part of it anyway. I think they may have mentioned the immune-related issues

but I am not so sure that cardiovascular was included in their plan. In other words, I think we ought to give a full sort of laundry list of things that they should look at in that five-year observationB-look for in that observation--

DR. PAXTON: Yes, there could be more. I was just actually trying to see if there was any way that we could give even more focus. There was a particular aspect of, you know, immune-related things but I think we are going in the right direction. Dr. Havens?

DR. HAVENS: Dr. Grant's approach to looking at the issues of myocardial problems associated with the drug I think were well taken and might give a prompt signal, if there is one, to people who were initially randomized to placebo and who might be on maraviroc. That is a particularly important issue in this drug which shows alpha activity in animal models, which shows decrease in systemic vascular resistance and, therefore, has a high biological plausibility in terms of the association with the myocardial ischemia that was

found. So, I think specifically focusing on that perhaps rare event in this population is very important.

Then, I knew that you wanted to include children and adolescents--

DR. PAXTON: Of course, I would never have forgotten that. Excuse me.

DR. HAVENS: That group of unrecognized populations, which is why I am kind of interested in the kinetics issue, and if the sponsor believes that the kinetics are important or not because often if we can just identify a kinetics target and do kinetic studies in younger populations, then that is a way to enhance the ability to use those drugs in different populations sooner. So, the kinetics issues become important.

Finally, we are still sort of on safety and who to study, there was some rhabdomyolysis. As I remember, three cases only in the maraviroc group. I don't know if they were associated with the increase in influenza and if the influenza wasn't really influenza. So, you don't know what

was really going on, but the fact that there was a little bit elevated CK and then the three rhabdomyolysis, which I think was just on maraviroc, makes you wonder about looking for that kind of rare signal as well.

DR. PAXTON: So noted. All right, Dr. Andersen?

DR. ANDERSEN: While we are talking about some of the recommendations, I would bring up again identification of historic groups, concurrent groups that are relevant to the populations being studied. You know, combination of some of the networks HCV studies. I mean, there is a group of subjects who are experienced on antiretrovirals who have HCV that are being treated for their HCV but there are placebo arms or control arms there as well. So, to be able to look and target those populations to be relevant for the studies so it is not an apples/oranges situation.

DR. PAXTON: Dr. Dee?

MS. DEE: I think that it was touched on down here. I mean, we are saying more HBV and HCV

but I think we need more work on people with liver impairment as well. I mean, I think they did like a one dose thing or one-dose study. So, people that, you know, have more chronic liver disease, more chronic illness related to liver disease than just viral infection.

DR. PAXTON: Dr. Rodriguez-Torres?

DR. RODRIGUEZ-TORRES: Yes, I think they should do PK studies in child C, severe hepatic dysfunction, and studies in co-infected hepatitis C patients, including cirrhotics and including those with child A and B, that they found no differences in the PK.

DR. PAXTON: Dr. McGowan?

DR. McGOWAN: Yes, I don't want to perseverate but I am actually concerned based on, you know, Dr. Grant's observations and the rest of the group about this hypotension issue and the use of erectile dysfunction drugs because I presume we are going to be giving this to sexually active adults who are going to be individuals with HIV for prolonged periods, who are probably in their mid

40s, early 50s, and we are already seeing perhaps an ischemic heart disease signal, and they are likely to go on boosted PIs. So, the combination of maraviroc, the boosted PI and the background risk factors might all lead to even more episodes of hypotension. So, I wonder if the company, the sponsor, might consider some sort of Phase 1 hemodynamic study looking at the interaction between erectile dysfunction drugs and maraviroc with sensitive endpoint analysis.

DR. PAXTON: Dr. Dee?

MS. DEE: Maybe too testing people doing these things with more strenuous activity than just getting up and down.

DR. PAXTON: Reality, right? Well, as Dr. McGowan has been proposing, you might get them after sex to see what happens!

[Laughter]

MS. DEE: I was going to say that but I didn't! But, you know, that is what we are talking about I think.

DR. PAXTON: Yes. Dr. Grant?

DR. GRANT: I think the best way to have addressed the race issue would have been to have recruited the study and to have insisted on a study that was representative of the U.S. epidemic at least. But absent that, I wonder if biological studies could be done to try to understand why this drug may have less activity in African Americans. They did look nicely at drug levels but this is a host-targeted drug so I think it would also be interesting to look at target levels as well, expression of CCR5 in different racial groups and under different circumstances to see if that may explain some of the trends that were seen.

DR. PAXTON: Dr. Dee?

MS. DEE: You know, it is so frustrating to sit here with drug after drug with not enough women, not enough people of color and, you know, there is always this tension about, well, we want to get the study enrolled and we want to find out what the answers are but we never have enough in these subpopulations of people.

So, I am wondering if we shouldn't

recommend something like the agency suggested or requested from Teva Tech, which is they were required to do a gender-based study after approval so we would still get the information in some of these special populations of people of color, Hispanics, people with HBV and HCV. You know, in other words, if you get your approval, at least we are not making you go slower but we are still making you find out what this drug is like in these populations without, you know, throwing a monkey wrench in the works but still requiring it. I mean, if we don't require it, it is going to keep being the same way.

DR. PAXTON: Dr. Birnkrant?

DR. BIRNKRANT: Thank you. It has been our policy actually to ask sponsors/applicants to enroll subjects that would parallel the epidemic, particularly those in the United States. And, when the data come in we seem to get not what we asked for early on in drug development. We are faced with that conundrum of, well, do we hold up the drug because we don't have the data in certain

populations or do we take a positive regulatory action and then ask for postmarketing. So, we are very frustrated as well, and it is our goal at some point in time to bring studies to this committee that adequately reflect the U.S. population.

DR. RODRIGUEZ-TORRES: I am going to just congratulate you. That is the only position.

MS. DEE: But we can ask them to do it in a postmarket fashion on these different populations.

DR. BIRNKRANT: That is true.

MS. DEE: You know, I mean, this way we will get it done finally.

DR. BIRNKRANT: That is one approach.

DR. PAXTON: Dr. Grant?

DR. GRANT: Actually, the way to get it done is to design it into the protocol. You can have stratified sampling such that you get sex and race balance. You can put that into the protocol and then you will get it.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: In terms of postmarketing surveillance and safety, just to go back to the

point that the original plausibility for this drug came from the observation of the delta-32 and there is information available, and there probably will be new information over the next several years about what this NAT mutation may or may not be associated with. Although giving a drug is different than being born with such a mutation, I would just ask that any postmarketing surveillance be targeted to diseases that are shown in other studies of genetics to be affected by this because I would think that many of these things would be otherwise very hard to pick out of a large database without specifically looking for them.

DR. PAXTON: Cicely and I were sort of discussing how best to do this and I think what we might do, since we are on question one, we might go ahead and just go ahead and have a vote, and I will summarize what has been said about the safety, what the panel has recommended here.

So, if we can just go ahead and vote first, do the safety and efficacy data presented support accelerated approval of maraviroc for

treatment-experienced HIV-1 infected patients with CCR5-tropic virus? What I am going to do is just go around and just ask each person to give their name and if they vote yes or no. I am going to start with you, Dr. Rodriguez-Torres because you are at the far end of the table-Band clarifications on what you are voting for.

DR. RODRIGUEZ-TORRES: You always start with me.

DR. PAXTON: Next time I will start on that side.

DR. RODRIGUEZ-TORRES: When I came here yesterday I felt this was an easy decision and it has become more difficult. But actually I was impressed by the quality of the data that the applicant presented, especially a lot of the studies that they did on PK interactions and, of course, the quality of the work of FDA.

I will say yes, with the following caveats, I think that I will be in favor that this drug has a label that expresses clearly the doubts that we have at this moment that we are very far

from answering, especially the possible rate of malignancies, infections, cardiovascular complications, and with the caveat that the sponsor is going to have multiple safety follow-up and has committed to studies to address the issues that we have entertained. But I think that the importance of the drug, a new drug for experienced patients at this moment is a "yes" for me.

DR. YARCHOAN: Dr. Robert Yarchoan. In terms of accelerated approval, I would say yes. The reasons are that there is a subset of patients out there that are resistant to all or almost all of the available drugs, who cannot get adequate treatment for HIV, and this drug, potentially combined with other drugs that may be coming out or may be available, would greatly help these patients. And, given all the caveats, I would say yes.

DR. WEISS SMITH: Sheila Weiss Smith. This is really a tough question but I would say for the accelerated approval that, yes, it does meet it, with the caveat that I think there actually is need

for a clinical trial post-approval, not just surveillance studies for safety. And, there was one thing that didn't come up with the efficacy data, which is what do you do when someone has a tropism switch and then switches back? Do you then try the treatment again? And, what are the implications of doing that?

MS. DEE: Lynda Dee. I would say yes, that the data presented supports accelerated approval. When I weigh the efficacy and the need of patients who have burned through everything versus the safety issues, which are more signals to me than actualB-they are more red flags than kind of hard substantive sort of-Bwell, they are not actually proved yet so they raise a red flag for me but they are not a deal-breaker. I guess that is the way to do it. But having said all of that, I vote yes only because we have this five-year study that is going to look at some of these issues that we discussed. But I would also say I vote yes and would require a postmarketing study to look at efficacy and other sort of issues for women and

non-whites and people with HBV and C. What a surprise, right!

DR. McGOWAN: Ian McGowan. I would vote yes for accelerated approval, with the caveat that the sponsor addresses some of the safety concerns we discussed this morning and this afternoon, and perhaps is a little more aggressive in terms of immunological surveillance. That would be my caveat.

DR. HENDRIX: Craig Hendrix. I would vote yes for accelerated approval. I think there is a clear and compelling clinical need. The efficacy is very clear and dramatically larger in magnitude than the safety risks that have been raised as possible issues, I think none of which have been defined, all of which will need to be addressed as we have listed but those are minor mitigating circumstances.

DR. GRANT: I would vote yes for accelerated approval. I think there is a clear need and some urgency to provide additional treatments that can protect our existing drug

armamentarium as people try to reestablish viral suppression. I do think more data is needed on races other than whites. I think we need more hemodynamic data. And, whatever surveillance is done should be active, and should be pathogen specific with respect to how this drug may affect susceptibility to very specific pathogens that may require CCR5 to act. So, I vote yes.

DR. GIBERT: Cynthia Gibert. I agree with what the other speakers have said. I would urge the sponsors and the FDA to look at rates of malignancies as people use the drug over longer periods of time. I think that there needs to be a better definition of a therapeutic window. I think the question of lipids and also interactions of statins, for example, with this drug need to be studied. And, I think it would be helpful to have as well defined causes of death as you can acquire in this study population.

DR. ALEXANDER: Barbara Alexander. I would vote yes for accelerated approval. But I think, you know, there is clear indication that it is

helpful for patients who don't have other options but I think the immunologic consequences are very concerning so we need close follow-up of those issues, which it sounds like the sponsor has plans for. I will say the issue for the clinician is what to do when the patient does fail and we don't have therapeutic drug monitoring available. Can we double the dose or we don't know because we don't know if they are failing because of resistance? So, it is a bit of a dilemma. The same thing with how do you treat a patient who has some degree of liver dysfunction, so dosing adjustments for liver dysfunction.

DR. PAXTON: I am going to vote last so go ahead, Dr. Havens.

DR. HAVENS: Peter Havens. I vote yes. I very strongly suggest that the drug is needed by a certain proportion of the population we treat, and I think that the benefits and risks clearly support its approval as soon as possible. I am very supportive of the suggestions that women, Blacks, Hispanics, age groups other than what were already

studied have studies done. And, the issue of better understanding the impact of kinetics and making drug available from a company so that other groups can measure drug levels might also be a useful approach to better understanding how to use the drug in different populations.

DR. ANDERSEN: Janet Andersen. I am voting yes for accelerated approval. I would ask both the FDA and the sponsor to look at the existing data on the Black race response rates, using undetectability as well as the viral load data; and that the approval and the literature surrounding the drug reflect those results pending the larger studies to come out. I think they also need to be targeted and not just passive surveillance to ensure that some of those data are gathered rapidly.

DR. PAXTON: I am also going to vote yes. I actually don't have anything more to add to the comments that have been made for future studies.

I think I have been asked to summarize just the general consensus. Obviously, the vote

has been for approval, accelerated approval of maraviroc, and the general consensus about areas in which additional data is needed and that Pfizer should provideB-I have been told that I have to specifically state that it was unanimous, the vote.

The specific areas we would like to see further studies in can be divided into population groups, disease states and various studies. And the population groups that we have urged the manufacturer to look more into are different races, African Americans, Latinos; gender; to children and, as well, to look at various effects of maraviroc in various disease states, such as the hepatitis co-infected or people with other types of liver impairment; possible myocardial impairment, the effect of hemodynamic effects of this drug on potential patients; to consider doing pharmacokinetic studies on children in these various groups; to also consider looking levels at target organs such as CCR5 by race and perhaps by gender. It was brought up that we perhaps need more information on CK and the question of

rhabdomyolysis in people who are treated; also the concomitant use of other medicines, particularly drugs used for erectile dysfunction. From the epidemiologic standpoint, it was also urged that we should have better identification of proper historic comparators for future elucidation of effects. We need to know more about some of the immune-related signals. There were also a few questions about dealing more with how will people manage patients on maraviroc given the current availability or non-availability of ways to actually measure serum level-Byou know the availability of the tropism assay. So, how would we actually manage people once this drug is made available.

Did I miss anything big?

MS. DEE: Malignancies.

DR. PAXTON: Malignancies, I guess that came up, yes.

We will go on to the next question. Number two is about safety concerns so nice a segue into this, there have been several safety concerns

during the development of all the CCR5 co-receptor antagonists including risk of lymphomas and infection, hepatotoxicity and tropism switching. Please discuss each of these issues with respect to maraviroc specifically, and provide recommendations for possible product labeling, postmarketing studies or postmarketing risk management strategies.

It is open. Dr. Havens?

DR. HAVENS: I don't know who is best able to answer this question. The data seem to support the suggestion from the slide that we saw that low trough may select for resistant virus. It is such a hard issue to deal with because there were so few of those breakthroughs. Do you feel like the data support that?

DR. WESTBY: As you say, there are so few cases I don't think we can make any firm conclusions. The one thing I would say supports Dr. Naeger's comment earlier that the 4 patients who were resistant to maraviroc and did have low levels, they also had no other active drugs. I

mean, sometimes it showed an OSS score but in all cases where that was done the patient was already receiving the drug prior to the study so there was no evidence that they were getting benefit from any of the other drugs in their regimen.

For two-thirds of the patients who were CCR5-tropic but showed no resistance and who received maraviroc, and the PK levels there were very variable and in most cases you could go and find times of poor compliance, so we actually think it is not low drug levels per se in those patients but, in fact, poor compliance that led to their failure, and that would be consistent with the fact that we found no resistant markers in those patients.

DR. HAVENS: Right, and this gets to the tropism switch question because the tropism assay doesn't identify 10 percent who are likely to have the wrong tropism identified by the assay. So, you get a month out, you see that your virus load hasn't changed. The differential diagnosis, as you point out, is that the patient wasn't taking the

drug, the initial tropism assay was wrong and just didn't pick up the CXCR4-tropic virus in the initial assay, or the drug exposure, given the dose with or without concomitant drugs, is inadequate for the problem at hand. So, it becomes a more complex issue in terms of trying to put it into practice. You can ask the patient are you taking all your medicines. You could repeat the tropism assay to see if you missed the 10 percent that might have been missed initially, and that would go to some of these issues, and then drug exposure for people on drug who are really taking it is something that we wouldn't have. So, how to use these issues in practice is tricky and I don't know exactly how to say do this study to show that.

DR. WESTBY: So, there were quite a lot of issues there. I can maybe try and respond to a couple of the specific issues which were raised a number of times around tropism, for example.

DR. HAVENS: That is what we are talking about.

DR. WESTBY: Yes. So, in terms of tropism,

when you say that 10 percent are missed, and we should bear in mind that this is in the context of the fact that the first tropism test did identify patients who either had dual- or mixed-tropic virus and they were excluded from the study at screening, and then there were a number of patients, I think 7.5 percent of patients who had a different result between screening and baseline. I think you were referring to those patients when you said that the assay may be mistaken.

DR. HAVENS: Or it was my understanding that the assay was accurate to within 90 percent and that it could misidentifyB-that the early selection for CXCR4 virus was because that had been present in a subpopulation that was too small to be picked up by the assay, given all those other issues.

DR. WESTBY: If I understand right, I think there are two issues there. One is what was the accuracy of the assay in those patients, or what are the prognostic factors? Is there anything which would distinguish those patients from the

rest of the population?

DR. HAVENS: Well, the specifics are if I do a test that shows CCR5-tropic virus and start the drug and the troughs are fine, what percentage will have had a CXCR4-tropic virus in a small subpopulation that will break through? I thought that was on the order of 7-10 percent. Did I misunderstand?

DR. NAEGER: Well, the assay is 100 percent sensitive to detect a minority of 10 percent mixture. So, if you want it 100 percent accurate you will only be able to detect to 90 percent.

DR. HAVENS: That is where I am going. That is where I got the 10 percent, from her.

DR. WESTBY: That isn't saying that in 10 percent of the cases you are missing a patient. That is saying that at the 10 percent level you are picking up 100 percent of the time. So, when we looked at the patients who switched between screening and baseline, we looked at a number of prognostic markers. We looked at assay performance over time. We looked at whether a patient was on a

drug holiday or not, whether the patient changed their viral load between screening and baseline. The only single factor that we could find which identified those patients as being different from the patients who don't switch between screening and baseline was that they had a lower median CD4 count. So, that CD4 count in that group was approximately 50 as opposed to 180 for the patients who didn't switch between screening and baseline. Also, the assay at the 5 percent level picks up virus 83 percent of the time, and the data that Dr. Naeger showed as part of her presentation and I showed as part of my presentation also supports that.

When we try to decide how many clones to look at in order to be able to pick up virus that may be there at very low levels, we would have needed 1,000 clones to be able to pick up a 1 percent incidence with 99 percent certainty. What we can't show because they were censored from the data are those patients who had CXCR4-using virus who didn't fail as part of the regimen. We did

include those patients who had a suppression in viral load. We had 6 patients in our detailed virology study, 2 of whom were on placebo and 4 were on maraviroc, who didn't fail virologically by week 24 who did have evidence of dual- or mixed-tropic virus.

DR. HAVENS: Six percent?

DR. WESTBY: No, we found 6 patients out of the 20. This wasn't a randomly selected group of patients.

DR. PAXTON: I am actually going to take a chairperson's prerogative here and try to redirect us a little bit. This has been a very good discussion. I think it actually relates a lot more to number 4.

We have been specifically asked to look at several specific safety concerns and they want us to discuss them as they put them out here, like what we think about the risk of lymphomas and infection, hepatotoxicity and tropism switching. So, to sort of continue in this line we can talk about tropism switching but it is in light of the

safety. You know, what are the safety concerns related to tropism switching possibly brought on by maraviroc?

DR. McGOWAN: I thought Dr. Dee summed it up nicely. I mean, we have seen signals that we have anxieties about and I think the sponsor has with due diligence laid out a pathway, very reasonable post-licensure type cohort studies, and I think we are going to make some suggestions for some very specific Phase 1 type studies to address certain issues, and I think we have already discussed that in a sense. I mean, we can make a list of those.

DR. PAXTON: Yes. Are there, like, any specific concerns about tropism switching that you would like to specifically direct the sponsors to look at now?

MS. DEE: You know, in my notes here-BI think that would just be better addressed all at one time in number four because that is a huge issue.

DR. PAXTON: I can deal with that. Why

don't we move then to talking about the lymphomas and infection safety concerns?

DR. YARCHOAN: I will just go back to what I was saying before. As the sponsor said in the beginning of the talk, this is really a new game with this class of drugs. I have been in some of the discussions about lymphomas with this and other things and I don't see a lot of evidence for an increase in lymphoma and, in fact, with the delta-32 there is some protection against AIDS lymphoma. But, clearly, the cytokines have evolved for some purpose and, clearly, there is evidence that they affect response to a variety of agents and they are involved in immune response to other factors. So, I think that for postmarketing surveillance and other studies one needs to really target those things for which there is a biological plausibility based on our evolving understanding of the chemokines, or epidemiologic evidence based on population studies. Breast cancer is potentially one of those, although the evidence may be early at this point. West Nile virus is one. And, one

question may be whether to put something in the insert, if people have symptoms of this whether the drug should be stopped, even though it is based on theoretic information at this point. Finally, that any surveillance really be targeted to pick things up because otherwise you will miss them in a general shotgun approach.

DR. PAXTON: Dr. Dee?

MS. DEE: I was looking at the question. So, it says please discuss each of these issues with respect to product labeling. Does that mean, in other words, they want language from us about, you know, the idea that this is a new class of drugs and that there is potential risk of immune dysfunction, including malignancies and infections and some risk of increased LFTs. I mean, do you want that language that is that specific?

DR. PAXTON: I will throw that over to Dr. Birnkrant.

DR. BIRNKRANT: Well, I think we are looking for recommendations in general. That is, how to include this type of information in the

label. We don't need really specific wording but more general types of terms.

MS. DEE: In other words, potential risk would be the term I would use because it doesn't say that it is happening but that it is a potential risk. The other thing that I just thought of that I meant to bring up before was people that have already had malignancies, you know, I mean, I think there might be some indication that this is not the answer for them. But that might be something else that you would want to add to that. But my language would be potential risk of everything we discussed and, you know, maybe a little bit about the mechanism of action that we discussed which would give you the basis for the idea that there is a potential risk. Do you want the postmarketing studies now or do you want to wait?

DR. PAXTON: Go ahead.

MS. DEE: You know, we were talking about EuroSIDA and cohort sort of strategy and then it came up that so what do we compare that to. I am wondering if we could use, like, the DA has cohorts

of people that include a lot of people with a lot of cardiovascular diseases so maybe we could use that as a comparator. And, I am wondering, Dr. Yarchoan, you know, I remember there has been a lot of talk at NCI always about this observational database of people with cancer. Is there such a thing?

DR. YARCHOAN: We do have databases in the Cancer Institute. There is the SEER database that captures cancers in I think approximately ten percent of the U.S. population. There can be an effort to match this. The epidemiologists at NCI have spent some effort matching this with the AIDS database to try to look at that. So, there certainly are a number of tools available in the Institute to look at some of these things.

MS. DEE: I mean, I know the sponsor has done a great job of looking at people in this population who have had cancer type events, but maybe those two databases could be used as a comparator. I mean, I would hate for them to study it for five years and say, oh, so what does this

mean, compared to what?

DR. PAXTON: I think Dr. Gibert wanted to address this.

DR. GIBERT: I would just make the comment that Boehringer-Ingelheim, after they had concerns about the increased rates of I think strokes and possibly other cardiovascular events with I guess tipranavir, actually had Dr. Justice from the VA veterans aging cohort study look at the VA database to look at rates of these events in the VA population, and presented that data I believe at the Croye. So, that is an example of industry actually using the VA data to answer questions which would be similar to some of the questions which might be raised in this population.

While I have the microphone, I just would make one other comment. For people who use these drugs, and particularly those maybe who have had resistance of whatever sort, are there going to be any recommendations for people who would require post-exposure prophylaxis to these drugs, either healthcare workers or sexual or drug-using

partners?

DR. PAXTON: I think it is something to bring up. It was actually in our briefing documents that this might be a potential use for this drug outside of the treatment-experienced.

DR. GILBERT: Well, not only to use it as preventive prophylaxis, like TENOFOVIR because it gets high gastrointestinal tract levels, but if I had a needle stick exposure to someone who had been on these drugs and had now a tropism shift, what would I do or what would I tell someone else?

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: The issue of malignancies had been raised and part of this is because some of the chemokines have been implicated in the immune response to some of the viruses that cause malignancies, and because of some of the findings with one of the other drugs that act in this class. Certainly, although the data here doesn't seem to provide any evidence for this, it is worth keeping one's eyes open in marketing for any changes. There have been so many changes in the epidemiology

of malignancies as HAART has become available and CD4 counts that one really needs to use current and simultaneous data rather than historical data to compare these things with. I think that is an important point.

DR. WEISS SMITH: As I am looking at the adverse events, they are not rare, less than 10,000 events if you look at the placebo arms of the studies. So, I am concerned about trying to find a comparator group, particularly a historic one when you have a population where these are treatment-experienced people and they do have high rates of other morbidities, whether or not it is even feasible to really pick out drug effects in any kind of cohort study. So, I would really push for a clinical trial, a randomized trial, even a large simple trial because some of these look like they are not that uncommon.

DR. BIRNKRANT: Can you elaborate a little more on that, please?

DR. WEISS SMITH: Well, I am looking at the population and, for example infection, if you look

at the FDA slides, we are not talking about something less than 1/10,000. You know, they are less than 10 percent in the placebo arm. So, if it is a common event, this isn't something that you would pick up or identify as linked to a drug in a spontaneous reporting system. You would just never find it. It is really the rare idiosyncratic. So, if you are going to look at the rates of these common events you really need to compare them to something contemporaneously. And, if you don't have a group that is very comparable, like a randomized comparator group, how are you going to tease out is it the drug, is it the dose, or is it just because the cohort I have on the drug I can't tell because they are different from my historic or other groups because no one is exactly alike? So, I am worried that without an experiment we may not be able to see for a long time, if at all, whether or not there really is something going on.

DR. ANDERSEN: I think what I am hearing, and I am trying to understand where you are headed with this myself, is that we are talking about

licensing a drug and it would be very difficult to now do a placebo-controlled trial. Perhaps what you are saying is what we have talked about with some of the issues of race and gender, maybe having some targeted single-arm or dose-findingB-or deal with some of these other dose questions that are being discussed in a trial so that you have routine collection of data and you can really look at it, and with a preplanned comparator group so that it is known where it is headed. Is that the direction you are going?

DR. WEISS SMITH: Yes, I think there are different strategies. That is absolutely a strategy but I think there are different strategies that you could use to try and get randomized comparators, even if it is not a placebo.

DR. PAXTON: Anything further on this issue? Go ahead, Bob.

DR. GRANT: Just on the hepatotoxicity issue, I would agree that the data from 1026 is going to be very relevant and worth looking at carefully with respect to the risk of elevated LFTs

specific for maraviroc.

DR. PAXTON: I have also been asked to see if we can specifically address the product labeling issues. So, basically in regards to maraviroc if we have any specific suggestions about product labeling for each of these concerns, for lymphoma, for infections, for hepatotoxicity. Is there anything specific that you would like to offer out there?

DR. HAVENS: Do you want to add myocardial ischemia to that list?

DR. PAXTON: Yes.

DR. YARCHOAN: Sorry, with lymphoma, I mean I really don't see any evidence of increased risk with this drug. There is a cluster of cancers that occurred with another drug of this class that really was not clearly due to the drug itself. I think there is a theoretic possibility because of the role of chemokines in the control of EVV. The rate of AIDS lymphomas is affected in delta-32. Actually, it is decreased. So, I think it is worthwhile perhaps pointing out some of this but I

don't see any evidence presented that there is an increased risk. Breast cancer is actually more of a concern, particularly because so few women were on these trials and they weren't followed long enough to see whether there is a change in the development of breast cancer.

DR. PAXTON: Thank you for bringing us back, we should be systematic about this. I think the first thing we should bring up is do we actually believe that there is a concern. I think that you are saying that for lymphoma you personally don't believe that there is a concern that would necessarily lead to a product label.

DR. YARCHOAN: Theoretic, but I don't see any data and I think, you know, it is a frequent enough event that you can say that the data doesn't show it.

MS. DEE: So, maybe we should say theoretical instead of potential risk.

DR. PAXTON: Similarly, they presented data to us that there was an increase in URIs and herpes infections and I think we have to weigh do we think

that that is significant enough that we should be mentioning it in the product label.

MS. DEE: We should stick with potential on that I think.

DR. YARCHOAN: With West Nile virus and perhaps I am affected by having seen a patient with this and all the confusion. It is a theoretic risk. It is based on the delta-32 but perhaps it is worthwhile mentioning that so a physician confronted with a patient might be alerted to at least stop this particular drug while it is being evaluated.

DR. PAXTON: Right, are you suggesting Dr. Yarchoan, that we should be a little more aggressive? Do you think on the label it should say if you have symptoms consistent with West Nile virus or pneumonia or something bad you should stop the drug? Is that what you are saying?

DR. YARCHOAN: You know, I have not been involved in all the negotiations on labeling and even with font zero there is always so much information that can be put on, so I will throw it

out as a possibility and let the agency use their wisdom in deciding. But having seen a patient with this who presented with increased neurological impairment and all the confusion—it was a postmortem diagnosis—if there is an increased risk, even theoretical, it might be worth alerting people to stop this drug while it is being evaluated.

MS. DEE: Is it West Nile? Really I don't know the answer to this, or is it tropical type diseases?

DR. PAXTON: I think it was specifically West Nile virus.

MS. DEE: Because a million things come over the internet and there are people that are saying that it is other types of tropical sorts of diseases, not just West Nile.

DR. PAXTON: But that wasn't actually presented in our background documents. I am presuming it is just West Nile. Bob?

DR. GRANT: Yes, I would advocate mentioning herpes exacerbation as a risk because

that is a treatable and manageable condition and potentially has epidemiological implications as well. And, the patterns were had a dose response and were relatively robust to the sensitivity analysis.

DR. PAXTON: It makes me kind of wonder, just as an aside, if you had somebody who had frequent hepatic outbreaks would that push you more to putting them on suppressive therapy if you are going to put them on maraviroc? Dr. Birnkrant?

DR. BIRNKRANT: I was wondering if Dr. Yarchoan could elaborate on the breast cancer association with blockage of R5.

DR. YARCHOAN: If I had a computer with Google here I could probably pull up something more quickly. It has been presented by Mary Carrington et al. That there is some increased risk of breast cancer in people with CCR5 variation. I know the company had some information. I think it is just worth really looking at the data carefully to see what there might be. I looked at the information presented. There weren't any cases of breast

cancer at all and breast cancer is not increased in HIV disease but, given the number of women and the relatively short amount of time the patients were followed, you wouldn't expect to see anything with this. But if people are on this for five or ten years it is conceivable that you might. I think you have to really look carefully at the data before assessing that. I just haven't brought all that data with me.

DR. PAXTON: Dr. McGowan?

DR. McGOWAN: I was just saying to Dr. Hendrix, it is just the hemodynamic instability and all the rest are theoretical that we need to be aware of, but I, honestly, am quite concerned about a patient with risk factors, diabetes, smoking, age, hyperlipidemia, boosted PIs and frequent use of Viagra. The other ones are actually going to drop dead on the drug. It won't be West Nile virus and breast cancer. So, I think that needs to be front and central at least until we have more data.

DR. PAXTON: All right, point taken. Well, what I wanted to just knock off because they asked

us what we feel about hepatotoxicity and then we should discuss more about the myocardial implications. So on hepatotoxicity, do we feel that there is an increased risk based on what has been presented today and what should be said on the label about this?

MS. DEE: I would say potential risk of increased liver functions.

DR. GIBERT: A lot of it looked as if it was concomitant use of atazanovir. I don't know if they looked at the data without atazanovir or what the hepatotoxicity or the increased LFTs would be. I would just mention that where it is used in more people with hepatitis C we see an increasing number of patients with very aggressive and frequently late diagnosis of hepatocellular carcinoma, and I don't know if this will have any impact on rates of development of hepatocellular carcinoma. That is just a caveat. I think if they took out the atazanovir, I don't know how that would affect the LFTs. Certainly, the bilirubin data would change. And prenavir.

DR. GRANT: I would like to rehearse the evidence that this drug actually has an effect on LFTs. I don't see it really in the data. What we do have is a few very frightening cases related to this drug and another related to the class. But in this drug there were a few cases that meet Hy's criteria, except for the fact that they were also on atazanovir, but atazanovir is not a drug which commonly causes both elevated bilirubin and LFT, as I understand it. And, then there was a case in 1026 which obviously went to liver failure and required a transplant. So, there were a few scary cases. I certainly have seen labeling along that line that, you know, even the overall data does not suggest an increased risk of LFT elevation, there are a few scary cases out there that clinicians should be aware or, especially in patients who have multiple hits on their liver already.

DR. ALEXANDER: Or who are on other concomitant hepatotoxins. Additional observation or monitoring should definitely take place in those patients.

DR. GRANT: Right. So, you get a patient with rising LFTs in the face of izoniazide, etc., you don't give her this drug.

DR. PAXTON: Dr. Gibert?

DR. GIBERT: I was going to say the same thing. If they are getting rifampin or if they are getting INH you would certainly use the drug perhaps with some caution.

DR. PAXTON: Well, it sounds sort of like a combined approach to me, that we want to indicate that this is a potential problem. That we want to certainly watch if somebody is on concomitant medicines that are hepatotoxic, but also in the postmarketing studies and the other studies they are going to do they are going to have to look at this much more in depth and, hopefully, in a few years we will be able to hone in on that a little bit more. But for now it sounds like we are urging that there should be something on the label talking about these cases that have occurred, and then perhaps urging that the people on other meds, who have other risk factors, should be more closely

monitored.

DR. HAVENS: But perhaps in the context that the data do not show hepatotoxicity above placebo for the whole group. I mean, we are getting into some theoretical labeling things here about the potential for possibly this and we do need to stick with the data that were presented and really go from the data, and the data don't show hepatotoxicity above background except, as Dr. Grant points out, in these scary case scenarios. How you say that I would leave to the Department, but there was no increase in overall hepatotoxicity except perhaps in unusual cases.

DR. RODRIGUEZ-TORRES: But then, on the other hand, there is the fact that scarce numbers of patients were co-infected, and that is also should be placed in the information in the label. On the other hand, these are not the classical patients.

DR. HAVENS: Right, so the concomitant medications or other risk factors are something that need to be borne in mind, but in a general

kind of way, compared to placebo there was not an identified risk overall of increased AST or ALT, both from the sponsor and from the FDA evaluation of that.

DR. PAXTON: In the interest of time, I am going to sort of try and push us along a little bit. One big issue that we wanted to talk about was the myocardial effects. This is something that we are adding onto what the FDA had asked us to talk about. So, I am going to open that up. Go ahead.

MS. DEE: I think the way I would pigeonhole these things is a theoretical risk or potential risk, and I think that we can apply different criteria to all the different conditions. You know, where we have seen something, for instance like if you mix and match this drug with IZONIAZIDE you may have a problem. In other words, there is a potential risk there. Malignancies, there is a theoretical risk. You know, I mean, without writing a whole wordsmithing here, we can put them in categories for the agency and say which

conditions should be in which category.

DR. BIRNKRANT: Also, in labeling we have also commented on areas where data are lacking so we can say safety and efficacy have not been established in child B and C or in co-infected. We can do that as well.

DR. PAXTON: Would it be helpful for us to quickly try and put that together for you now? Some of this already has come up. We have already heard that we are lacking efficacy data, and all that. So, we could pull that from what has been discussed already.

It seems that it is roughly falling out that we think lymphomas are a theoretical risk, not an actual risk. We think that infections-Bfor some things it looks like they are, you know, a natural risk, for URIs, for herpes simplex, for West Nile virus. For hepatotoxicity, you know, it sometimes falls into potential risk. In that, you know, the general thing has not shown any problems but, as Bob says, there are a couple of scary cases so maybe it is between theoretical and potential.

Then the myocardial thing is what I would like us to sort of finish off with right now, to discuss what we feel about that right now in terms of what we recommend to the FDA to either say or not say about it. Dr. Andersen?

DR. ANDERSEN: Statistician, not a clinician, and I am actually not addressing that but just bringing up something else that the FDA and the sponsor may want to consider looking at in the data. A number of the presentations have made a heroic attempt to try to deal with the problem that in this study on the placebo arm there is less follow-up, for very legitimate reasons. And, by doing a time adjustment that acts as though the out weeks and months on placebo are the same as the early months and weeks, the period of high toxicity, so may over-adjust. So, one thought is to do a landmark analysis where you are looking just at the first 12 or 24 weeks when a lot of people have a lot of follow-up. I am looking specifically at the table of cardiovascular events. If this were in the first 4 weeks, then the

difference that is in the tables might actually be different. If, in fact, what is going on is that the extra follow-up in the maraviroc arms is leading to more events, it could go away. So, I would suggest looking at the time component here, potentially in landmark analyses, potentially some other way.

DR. PAXTON: Shall we discuss more about the myocardial effects or do you feel like you are talked out?

DR. HAVENS: It might be best phrased as cardiovascular because there was postural hypotension and myocardial risk which may be exacerbated theoretically by use of other vasoactive drugs.

DR. McGOWAN: It is a little more than theoretical.

DR. HAVENS: Oh, yes, absolutely.

DR. McGOWAN: In Phase 1 it is the dose-limiting toxicity, and I think even when they did the subanalysis looking at the concomitant administration of hypertensive agents I thought

there was a bit of a signal there, actually. So, I think something like saying, you know, Phase 1 studies have demonstrated hypotension as a limiting toxicity. Therefore, clinicians shouldn't be prescribing hypertensive agents, including drugs for erectile dysfunction may result, you know, in cardiovascular instability, or something.

DR. HAVENS: Well, the preclinical data support that as well because of the alpha agonist effect.

DR. PAXTON: Dr. Dee?

MS. DEE: So that should just say risk.

DR. WEISS SMITH: Similarly, in the FDA presentation they talk about CPK elevation and rhabdomyolysis and that probably should be there also.

DR. PAXTON: So noted. We received a note up here asking if we could have a brief break after these discussions. So, maybe about ten minutes? About a ten-minute break and then we are going to come back and we are going to go on to questions three, four and we will try and touch upon five if

time allows. Thanks. We will see you back in ten minutes, which will be 3:35.

[Brief recess]

DR. PAXTON: We are going to start in on the remaining three questions. Moving right ahead, question number three is do the data support the applicant's proposed dosing? Please consider the recommended dose in light of the exposure-response modeling.

I think just to summarizeB-I don't want to do this wrong so Pfizer can correct me-Bthe proposed dosing is 300 mg twice a day in the absence of PIs and 150 mg twice a day with certain PIs, with the exception or ritonavir and tipranavir. Is that correct?

DR. MAYER: I am sorry, can you repeat the question?

DR. PAXTON: Since you are standing, could you just state for the group what is your proposed dosing so that we can vote on whether or not the application supports that?

DR. MAYER: Okay. Can you, please show

slide 148?

[Slide]

This is what Dr. Dunne presented earlier today. We are seeking approval of maraviroc in combination with other antiretroviral agents for treatment-experienced patients with R5-tropic virus. So, patients would be dosed with maraviroc at 150 mg BID with all protease inhibitors excluding tipranavir, ritonavir and delavirdine; 300 mg BID with tipranavir, ritonavir, nucleoside or nucleotide analogs and enfurvitide and nevirapine; and 600 mg BID with efavirenz in the absence of protease inhibitors.

DR. PAXTON: Dr. Gibert?

DR. GIBERT: May I just make a comment?

DR. PAXTON: Yes.

DR. GIBERT: Are you going to have any data on derunavir or the new Teva Tech NNRTI?

DR. MAYER: We do have data with derunavir and the data with derunavir is consistent with all the other protease inhibitors, excluding tipranavir/ritonavir, in terms of the requirement

to have the unit dose to 150 mg. It is in the same range as the other protease inhibitors in that category.

DR. PAXTON: Well, the question posed to us is does the data support this recommended dosing. I am almost a little hesitant to bring it up because we talked about so much on the whole issue of boosting and whether or not that should enter into our potential recommendations to the FDA about whether or not anything more needs to be done on this.

Just to simplify things, I might ask if there is anyone here who thinks that the data does not support the recommended dosing?

DR. GIBERT: Can I just make a comment?

DR. PAXTON: Yes.

DR. GIBERT: Does this impact the ongoing studies, 1027 and 1028, in terms of the dose that the patients are on?

DR. PAXTON: I am sorry?

DR. GIBERT: Does this decision about the dosing have any impact on the current, ongoing