clinical trials where people are getting the drug once a day?

DR. PAXTON: I can't answer that question. Someone from Pfizer?

DR. FELSTEAD: The studies are reaching their week 48 endpoint and then the intention would be that we would unblind the patients and the investigators at that time. I would guess this would coincide with discussions with the agency as to what the recommended dose is and that would then influence what happens to the patients. They will still remain within the trial. As we said, we are intending to follow them through week 96, till the last patient reaches week 96. So, I would think it would be a coincidental occurrence.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: Just a question, do we have data on the 600 BID for subjects who are taking efavirenz, or anybody?

DR. HAVENS: And on 300 BID with nevirapine. Did we see those data? No, we didn't see the data.

DR. HENDRIX: The nevirapine data was presented to us and it was in the package. And, the package was somewhat discordant with the original recommendation, which they have now revised so that there is not a revised dose for nevirapine, if I understand it correctly. But we were shown the data.

DR. MAYER: Just a clarification, we have data on 600 mg in healthy volunteers with efavirenzB-sorry, correction, we have no data with the 600 mg dose.

DR. ANDERSEN: So, that is the one that is based on modeling only with no data actually? Okay.

DR. FELSTEAD: There is a drug interaction study where we dosed maraviroc to steady state, efavirenz to steady state, and showed a 50 percent reduction in maraviroc exposure, and then doubled the dose of maraviroc and that overcame the induction of efavirenz. So, it is based on a thorough drug-drug interaction study.

DR. PAXTON: As this is a yes/no question

we are going to have to go around and ask everyone individually for their vote. But I want to make sure, has everyone had a chance to ask further questions of Pfizer about the data before we go around and ask everyone for their individual vote? Of course, you are always allowed to put in caveats to your vote. Go ahead.

DR. HENDRIX: Is this where we should talk about the TDM issue which is what a lot of the questions had to do with, with the therapeutic drug monitoring issue? I mean, my read of this is that what they proposed is reasonable. But it seems to me that in some percentage of patients that have low concentrations--and we can quibble about whether that is less than 50, less than 75 or less than 100B-there is a clear benefit based on the exposure-response data for increasing them to a higher range. It may be 2 percent on a population basis, but for those individuals, they are going to go from a risk of resistance, and there is data for that, to being in a range with everybody else where they ought to be. So, exactly how you

operationalize that, I don't know because you don't have a drug that is commercially available but as soon as you recommend that drug levels be used to target doses there will be a market that develops very rapidly for having those available.

Chicken or egg, I don't know how you do that but it seems to me the data is compelling for that, and the number you choose is different depending on whether it is the FDA's data, which is a multivariate analysis where they presented one of the variables, or Pfizer's though I am not quite as clear on exactly how they did it but I think the data strongly supports that and that needs to be part of the dosing recommendation.

DR. PAXTON: Dr. Anderson?

DR. ANDERSEN: But I think it is important not to get turned around. In the absence of any drug levels, to just say somebody did not get a good drop, double the dose. You know, you don't want to go there. You do want that TDM. You do want that monitoring before anything is done.

DR. PAXTON: Dr. Havens?

DR. HAVENS: We have to be very careful before we recommend TDM. I was perhaps the most pointed in my discussions this morning, but we maybe have to ask the FDA what data are they asking us to use to make the evaluation of whether or not we recommend this dose or not. Classically, the pharmacodynamic data are not used to make a dosing recommendation for the FDA. That led to the standoff this morning when I turned down the chance to see the slide again.

There might be issues about how to get the best drug concentration, but if we believe that early approval of the drug is appropriate what we are basing that on is we used this drug with these other drugs in these doses, and this was the clinical response, both for efficacy and safety. Therefore, I would argue that the question that we are perhaps asked to address is based on the clinical outcomes data at 24 weeks, which is short and may not be enough to show the effects of low C-trough at 48 or later weeks so it might not be optimized for each patient. But if we believe

there should be rapid approval we have to based that on the clinical data I think, as irritating as that may be to me personally.

DR. HENDRIX: I agree with thatB-you mean virologic data. The virologic data supports the overall dosing recommendation. It also supports--

DR. HAVENS: Right.

DR. HENDRIX: B-in specific subsets, those that have low concentrations, also the virologic data, the same data that you use to approve the drug in the first case, in the first question, is the same kind of data that supports the value of some kind of drug monitoring to get into a range that is associated with higher frequencies of response.

DR. HAVENS: No, they didn't show that.

DR. HENDRIX: No, it is there. Both the sponsor and the FDA showed that data this morning.

DR. ANDERSEN: Showing an association between observed drug level and response is not the same thing as saying if you take a non-responder and increase their dose, then they will respond.

DR. HENDRIX: I agree. Then what we can do is do this prospectively and require that they do a TDM study. I don't know how large it would have to be. It seems very large. But, you know, there are decisions made on those kinds of associations all the time and this is perhaps the best example we have in antiretroviral therapy to have this data this early to actually do these kinds of things. There is a huge market for TDM where it is not indicated and there isn't sufficient data. It appears to me there is a lot of data here that we need to deal with in one way or another at least so the agency can sort out specific recommendations either for postmarketing studies or for dosing recommendations.

DR. ANDERSEN: I think the data here are spectacular for hypothesis generating on the subject and, interestingly, the study to show that is actually quite small because you are taking people who are failing. If you do something and they immediately respond, you know, signal is instant.

DR. HAVENS: The other part of the problem is that if you are already on one of the boosting combinations you are more likely to have drug concentration that is within somebody's therapeutic range. If you are on the 300 BID without any of the boosting combinations, most of those people were on tipranavir/ritonavir which didn't overall lead to a higher trough, no data were shown to say that doubling the dose there would get you into the therapeutic concentration for C-trough. Were there? Did the company show those data? So, the people who are most likely to be in a low C-trough are the people on 300 BID who also were getting tipranavir/ritonavir. I don't think we saw data showing the effect of doubling the dose even on C-trough, let alone outcome. Those people are already special because they have a lower C-trough.

DR. HENDRIX: There are lots of ways to skin a cat.

DR. HAVENS: Right.

DR. HENDRIX: If you increase the dose, by just increasing the dose of the primary drug,

maraviroc, you will get an increase in concentration. How much, you will only know by doing monitoring to find out--

DR. HAVENS: But you may get different amount of increase depending on the background drugs that you are on.

DR. HENDRIX: Absolutely, and the FDA has made one stab at this with a one-time only doubling of the dose, and that is a nice place to start.

DR. HAVENS: But that was all theoretical. There was no data for that.

DR. PAXTON: Fascinating discussion here. Go ahead, Bob.

DR. GRANT: Were the C_{mins} that we saw measured here, was it after an observed dose or was it a random sample or a pre-dose sample?

DR. JADHAV: In the clinical trials sponsor collected sparse sampling so patients gave anywhere between 2-15 measurements of concentrations. Based on that, the pharmacokinetic model that was developed from the Phase 1 until the Phase 3 was used to predict. So, for some patients the C_{mins}

were available at their failure or, if not available, were predicted based on the model.

DR. GRANT: So, it was sparse sampling after an observed dose.

DR. JADHAV: Yes.

DR. GRANT: Well, that is actually helpful and I think there is enough to advocate for a properly designed study to evaluate the utility of TDM in this setting, but I would agree that there is not enough data here to recommend it at this time.

DR. PAXTON: I think what I am hearing here is that there are substantial concerns on the part of committee members about other things that need to be done in terms of determining what correct dosing will be, under which circumstances. So, what I think we should do, we are asked to vote on what we think about whether or not the data supports the applicant's proposed dosing. But I think we should also be offering suggestions as to what these further studies or investigations should be.

Dr. Andersen has said that one of them would be relatively easy. You offered a study design. So, what I would suggest is to take a couple of minutes now and just put out what you think the best study would be, and then we go around and we do the yes/no vote that the FDA would like us to do. So, if anyone would like to sort of propose what you think the future studies should be about the dosing.

DR. HENDRIX: You can sort out the size, but I think if you have just a one-size-fits-all, one for a man, two for a horse kind of dosing, that is one arm. The problem with all these is always the blinding but you can also build in blinds and switches for the other. Then, there is one where you have to figure out some kind of approach, whether it is doubling the dose one time or giving a couple of doublings, or something that would seem safe within a certain range, and control those two. I don't know what kind of event rates you are going to look at because your outcomes are going to be virologic change. That is the only relevant

outcome for that study beyond toxicity as well, of course. You want them on both sides of the coin.

I think saying anything more than that would be very difficult in terms of exactly what you are strategy would be, but I think, you know, the agency is onto a useful approach to start this. I would allow more than one step in doubling it and I would look very carefully at this data because it seems to me that 50 is too low and 75 or 100B-I mean, this thing peaks out at 200 but that may be getting too high on the toxicity side. But, you know, look at the data that you have to pick what kind of a threshold, how many steps you might allow to build in because you don't want to take forever to get there and do that and compare it. Because your outcomes primarily are virologic, I am not sure that the expense of blinding and all the difficulty you have to go through is necessarily worthwhile, but I will let others sort that out.

DR. PAXTON: Anyone else like to offer an opinion? Dr. Andersen?

DR. ANDERSEN: Actually, I agree with you

that especially those first studies can be quite simple. Somebody has failed to achieve a response. Double the dose. You are expecting them to stay stable. If they drop their viral load again you have positive signal.

It probably will be important to do some smallish randomized studies with placebos for purposes of sorting out adherence, or to have done MEMS cap. I mean, there are other ways to deal with the adherence issues. But I think these studies are actually quite modest in size.

DR. PAXTON: Dr. Dee?

MS. DEE: I wonder, if somebody is failing could you randomize one to a double dose and one to do therapeutic drug monitoring and see if that--

DR. HENDRIX: My concern-and this is why I said I think it would be a large size-my concern with only starting with those that fail is that if they are like the four or five that are resistant they are out. There won't be any way to show a change. You can increase the dose until the cows come home and they may have no benefit.

DR. NAEGER: They are also going to have to be R5-tropic.

DR. HENDRIX: I am sorry?

DR. NAEGER: They are also going to have to be R5-tropic.

DR. HENDRIX: Yes. That goes to question number four. So, that part is complicated because I think if they fail to respond they may already be resistant, or the fail because they are emergent, therapy have an X4 emergence that has occurred, which may or may not be a different issue. I don't know the concentration relationship for those in particular. So, I would be cautious on what the inclusion would be and the failures may be a particular problem already.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: I was going to say a very similar thing, that a patient who is failing a drug is different than a patient that is starting off and is getting a different dose because they may have emerging resistance. A failure to respond to a higher dose doesn't mean that the higher dose

wouldn't have worked better if it was started initially.

DR. PAXTON: Dr. Gibert?

DR. GIBERT: Is there any evidence for any weight-based dosing, and does anyone know anything about the role of grapefruit juice when taking this drug?

DR. FELSTEAD: I don't think there is any impact of weight over the patients range of weight that we have studied. As for grapefruit juice, I guess the CYP3A4, inhibitor, it would be a mild one. We have not done a specific study looking at grapefruit juice.

DR. HENDRIX: One last comment on the dose that I just want to raise as an issue is that the food effect here, to me, seems to be really fairly large. There is no recommendation to adjust. It is a third of the concentration. The data shows that there is a concentration exposure relationship so I am not going to make a firm recommendation on this because we don't have a prospective intervention to show that it is a benefit, but I am

very concerned that that is a significant change and, you know, what is the downside of having it in? It may complicate the labeling and it may complicate a patient's schedule with this but, you know, it is a third reduction in the concentration. To me, that seems kind of large to ignore in the labeling.

DR. PAXTON: We are going to go around and vote now, but I think it should be noted that there has been considerable discussion from the panel about a need for doing other studies, and there has been a caution about carefully choosing which patients should be included in the study, that not necessarily depending only on failing patients will give you the best study population.

I think we should go around now and vote yes/no as we have been asked on this. If you have additional caveats, feel free to put them in. This time we will start on this side of the table. So, Dr. Andersen, you are up first.

DR. ANDERSEN: Janet Andersen. I approve of the dosing as outlined here, with the caveat

that the additional studies be done. What I do not at this point support is the recommendation of doubling the dose until we see some data on that in subjects.

DR. HAVENS: I support approval of the dose as recommended by the sponsor based on the presentation of the clinical data, and would hope that they will follow out the current studies for a long enough time to see the potential for the late effects or the effects of a low trough on late failure, and further support intensive studies of the relationship of PK and clinical outcome so that we can better understand those relationships. I, likewise, cannot support a recommendation for changing the dose in response to a low trough since we don't have any data to show what would happen to the exposure in the face of a changed dose, or a changed boosting regimen like the addition of saquinavir or ketoconazole or delavirdine.

DR. ALEXANDER: Barbara Alexander. I would vote yes for the applicant's proposed dosing, with the caveats already mentioned. I think it is very

important to sort out the way and whether or not it is going to be possible to use therapeutic drug monitoring for the clinicians trying to take care of these patients.

DR. GIBERT: Cynthia Gibert. I approve the requested dosing as they have outlined it, with the caveat that I think when this goes into clinical practice clinicians are going to have to think of the cost of therapeutic drug monitoring, tropism shift assays, phenotypic and genotypic resistance testing, CD4s and viral loads to sort of use this drug properly along with other therapy.

DR. GRANT: I think the data supports the proposed dosing in white men.

[Laughter]

The relationship between C_{min} and efficacy may be different in different racial groups because of differences in concentration of the receptor or in competing cytokines. The relationship between C_{max} and a given dose may also differ depending on body habitus. Asians in particular ought to be studied with respect to dose reduction strategies

that may be warranted in people with smaller body habitus.

DR. HENDRIX: Craig Hendrix. I vote in favor of the proposed dosing, with the comment that it is suboptimal and I think there is a benefit of increasing the levels in some subset of patients based on the data that has been presented, and concur with the recommendations for a concentration-driven management study to follow soon thereafter in folks that are naive to maraviroc.

DR. McGOWAN: Ian McGowan. I approve or the sponsor's recommended dosing strategy.

MS. DEE: Lynda Dee. I would say yes to the dose, no to the double dose, yes to further studies and yes to therapeutic drug monitoring, maybe in a subset of non-whites and women in that postmarketing trial that I hope the sponsor will undertake.

DR. WEISS SMITH: I agree with the dosing, the 150 mg and 300 mg. The 600 mg dose, I am concerned that we have modeling for the

effectiveness but not for the toxicity endpoint so I would like to see that data. Also, a question about if there is a dose somewhere between 300 and 600, if it does become toxic, that might be better.

DR. YARCHOAN: Bob Yarchoan. I support the sponsor's initial dosing, with the caveat that there is really no data on the 600, and wonder if a lower dose might be better as an initial one there; and with the caveat that, as Dr. Kuritzkes says, with the goal being to really suppress the virus, I do have a concern that we are going to be under-dosing a number of patients and this will show up in longer studies; and highly support additional studies to optimize the dose in all people so we can have greater guidance on this.

DR. RODRIGUEZ-TORRES: Rodriguez-Torres. I agree with the dose recommendation and with everything that has been discussed. I think that this drug has the potential to be much better for the individual patient but much more information is required in every patient that we don't have at the moment.

DR. PAXTON: Lynn Paxton. I also agree that the data support the manufacturer's dosing. I have no additions to the caveats that have already been expressed.

The vote has been unanimous for this and we will now move on to the next--

DR. HAVENS: Can the FDA require that the company make drug available for different companies who might want to do TDM?

DR. BIRNKRANT: No, but we can strongly suggest that.

DR. PAXTON: And when the FDA strongly suggests people listen. Right? All right, number four. We have actually started talking about a lot of this. I would urge people not to repeat things that you have already said, in the interest of time.

Number four, the Monogram Trofile assay was used to screen subjects for enrollment and to monitor subjects for tropism switching. Please discuss how you would recommend assays for tropism testing be used for the management of subjects who

might receive maraviroc in clinical practice.

As an addition, one thing we also said we would kind of defer to this time was to talk about any particular safety concerns you might have associated with tropism switching. Dr. Hendrix?

DR. HENDRIX: To me, there are two phases. One is initiation; the second is management while on therapy. It seems to me that the initial decision is based in the same way the studies were done. I don't know where they are going to get it if it is not commercially available, but wherever they can get it, they need to be, you know, pure R5 then they can go onB-if they are not, not recommended they can go on. But the big concern there is that there will be some population, a subpopulation, up to ten percent based on the assay, or maybe somewhat less than that, that are not going to be responsive and if they are being optimized, adding in maraviroc and some other drug, which is the way the scenario will probably work they are really only adding in one drug given that subpopulation, and that would be a problem. You

would like to know you are adding in two. So, for sure, if it was resistant because it was dual or mixed, you wouldn't do that. So, you want to have that.

For management it is not so clear. But I think probably for the same reason you would want to be sure you are on two good drugs for all the viruses you knew you had. So, if you switched to dual or mixed, again, you would probably stop or at least re-optimize in some way based on that information. But this, of course, all depends on availability of that information. But I think those are sort of the two check points for how you would use those.

DR. PAXTON: Can I follow-up on that? Would you take the next leap and say that if this assay, by chance, is not widely available by the time that maraviroc is approved that that should affect whether or not maraviroc is used?

DR. HENDRIX: I think it is risky if you don't know that they are dual-tropic, and weren't the numbers like 50 percent of those that were

screened for this were dual? I mean, yes, that is 50 percent. If you think you are adding in two drugs and you are only adding in one, I think that would be very dangerous.

DR. PAXTON: I think we might put that as a safety concern. Dr. Dee?

MS. DEE: I think Monogram has said that it will be ready. That being said, obviously before initiation, but management-BI mean, I am not sure. I think it is a huge issue. I have here 47 and then I have 32, I don't know, large percentages of people failed the drug at the same time there was a shift for people that were on drug. So, you know, not only are we talking about resistance and not only one drug, but maybe outgrowth of X4 virus that might be more dangerous and might do a lot of damage. I just wish we had a better assay and I think if this drug wasn't so-Bthe efficacy wasn't so clear that, you know, I might say, wow, we shouldn't do anything to approve this. So, for me, the issue is-Band everybody, and I am supposed to be giving answers but I don't know how anybody can

say how you should use this as a management tool at this juncture with what the virus doesB-excuse me, what the test doesn't do for people with viral load under 500 for instance. So.

DR. PAXTON: Dr. Grant?

DR. GRANT: Just in terms of how to use the test, I think there is some evidence here that you would want to check the Trofile test at two different time points because there were something like seven percent who scored R5 only at a screening test, and then dual-tropic at baseline, and then they responded as those who were dual-tropic from the beginning. So, it looks like, for whatever reason, either variation in the assay or variation in the amount of X4 present, that checking the tropism at two different time points would make sense to make sure you are starting the drug in someone who has a good chance of responding.

I would add that I would be interested in knowing more about genotypic patterns associated with tropism. Were there any mutational patterns

in the V3 loop that predicted virologic response comparably to the results with the phenotypic assay that was described. There are algorithms for predicting tropism from genotype. They function more or less well. It would be interesting to be able to look at how well they function in predicting virologic response in the context of these trials. Genotyping V3 is technically going to be easier than phenotyping V3 but for now I think the only data we have is from the phenotypic assay and, you know, that would be appropriate for the label.

DR. PAXTON: Well, I had something I didn't quite understand. I think, clearly, there was a theoretical concern that with a tropism switch from R5 to X4 we might see worsening disease progression. However, they also showed us data that there is a relatively quick reversion, once the drug is withdrawn, back to R5. So, it is not clear to me what will actually happen in real life. Will that period of time in which they are predominantly X4 have an effect on their actual

disease course? So, I would think this is something we would want to watch in these postmarketing studies that we are proposing for them. Dr. Weiss Smith and then Dr. Andersen and Dr. McGowan.

DR. WEISS SMITH: My question is even if we have the assay, I understand it takes quite a while to read. There is several weeks lag. Is that true? I am wondering how often it would even be used. In other words, would this be something that, once it is out, people would just give the drug and see if there was a response, and then follow it and then, you know, if it stopped working then do a test to see if it changed? I am just wondering practically, if it was expensive and time consuming, if it would actually be used even if it was on the label.

DR. NAEGER: I can just clarify that the assay does take two to three weeks turnaround.

DR. PAXTON: Dr. McGowan?

DR. McGOWAN: Just going back a step, you know, certainly viral transmission in my lab where

we routinely infect goat explants, they are happy to be infected with R5, X4. Absolutely no problems. And, the viral kinetics may vary. We have a paper coming out in AIDS in a few months comparing tonsil to rectum, but the reality is I can't but believe that everyone who is HIV probably harbors X4 already. But the interesting thing is why, actually, when you apply R5 antagonism everyone doesn't flip to X4 that quickly. I think that probably says more about what we don't know than what we do know.

So, constructing complex algorithms around the possibility, I think it is going to be fascinating to see data from patients who have been on the drug for a year because I think we may find those numbers may change. I say all of that in the context of how much importance we place on the Trofile assay because, you know, I think we may be revisiting the whole thing in six months.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: This is just a question about how long harboring predominantly X4 is a bad

thing. In other words, is there an urgency to find out early if somebody is flipping. One thought would be, as part of surveillance, if people are coming off study early for other reasons, toxicity or something like that, with detectable virus, is to check tropism then and see what is happening. Whether everybody is just starting to show some X4 and things like that. I mean, it is almost free other than for test kits.

DR. McGOWAN: The Trofile is likely to be free?

DR. ANDERSEN: No, no, I said it is free other than. It doesn't require a new study. It is a way to begin to see what is the pattern for switching.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: As I alluded to before, I think the availability of this drug and what we are learning really points out what we don't know and some interesting questions. R4 virus is associated with a worse course but it may be that the worse course, in part, helps select for the R4. You

know, the other question is what keeps the virus more towards R5 in people with earlier disease. So, I think there are a lot of questions here and, hopefully, the availability of this drug will in part add to our understanding and lead to an understanding of the biology, which will then inform how to best use this drug and I think it is going to be a learning curve.

The other thing is that it is conceivable that an inhibitor of virus that is R4 is added to the armamentarium and that will change the whole ball of wax. But that is obviously a discussion for another day.

DR. GIBERT: If you look at the table in Dr. Naeger's discussion, on page four, when people failed therapy--this is at only 24 weeks of therapy--actually the people with BID dosing of maraviroc had more failures than those with once a day dosing. Also, I don't know what it means when they have dual/mixed-tropic virus. Is that different from just having a CXCR4 virus in terms of implications for disease progression? I don't

know if Pfizer has any thoughts on that, or the FDA.

DR. DUNNE: We can talk a little bit about whether there is a difference between response and X4 dual-tropic. I think in general, we need longer follow-up and I think we have said before we are committed to obtaining longer follow-up on patients who have had a switch even transiently to see what might happen. That switch will be either with X4 of dual-tropic or mixed-tropic types of viruses.

DR. GIBERT: I mean, we have seen that the dual/mixed will go on and select the CXCR4 unless somehow it was suppressed or the drug was stopped.

DR. WESTBY: If I could show a figure that I think is in the briefing document that may address the question, which is T-3?

[Slide]

This may not address your question so, given the time, stop me early if it doesn't. I think the question you are asking is, is there a difference in the assay results between dual/mixed or X4. As we put in the briefing document, in a

pure population of virus, as shown on the top of the screen, a virus will be called X4 in the assay if it only infects X4. It will be called R5 in the assay if it only infects CCR5 expressing cells. And it will be dual-tropic if it infects both cells, which is shown in the middle.

The situation in patients, as a number of groups have shown and we have presented today, is somewhat different in that you have a mixed population of viruses, which is shown on the bottom. So, you can have a mixed population of virus which has X4 and R5, that has R5 and X4 or has a mix of R5, dual or X4.

[Side]

I think what our data supports is in patients what is happening with maraviroc is, on the top slide, in a pure population you will take out all the CCR5-tropic virus. In the bottom case, the outcome of the assay will depend on the population with which you started. So, on the right you go from dual/mixed to X4 because your population had a mixture of CCR5-tropic virus and

CXCR4-tropic virus. As shown by the blue crosses, once the CCR5-tropic virus is removed all that is left to detect is the CXCR4-tropic virus.

As Dr. Mayer presented earlier, when we looked at different outcomes where the patients were dual/mixed- or X4-tropic in the 1029 study, we still found CD4 increases in both populations. So, in all of our analyses that we have presented to you today we have been careful to term CXCR4-using because in all three cases along the bottom there is still presence of virus, whether it be the total population or part of the population that can still use CXCR4. So, any patient in our study during screening that was DM or X4 was excluded from the study and only those patients in which we only found CCR5-tropic signals were included.

I don't know if that helps the discussion or not but that is where a different result be the outcome of the assay, but the outcome in terms of clinical outcome appears to be the same. In those patients, as I showed in my presentation, when we follow them up, whether they were X4 by the assay

or dual/mixed by the assay, once maraviroc is withdrawn then the CCR5-tropic population in the mixed population appears to grow back and the virus becomes CCR5-tropic again sometime afterwards.

DR. HAVENS: But when you say the outcome is the same, you didn't mean that if you used that in a CXCR4 population the outcome was the same as if you used it in a CCR5 population to begin with, did you?

DR. WESTBY: No, absolutely not.

DR. HAVENS: Good. Thank you.

DR. PAXTON: Dr. Birnkrant?

DR. BIRNKRANT: I also wanted to clarify, again relating to the use of the tropism assay, should we be considering the use, in addition to baseline, at any time point where patients would meet definitions of treatment failure as described in the protocols, or even earlier than that should we obtain an assay at that point in time? Should that be put into the label or not?

DR. PAXTON: Dr. Hendrix?

DR. HENDRIX: It seems to me that at least

when you have either a viral load change or CD4 change suggesting failure, and likely you will have one of those well before the other, at those times you want to have it to confirm that explain that that is the reason or it is not the reason. But if you really want to understand the biology of it, you have to have it more frequently than that. That is why I think that can only be done as part of a prospective study specifically looking at this. But that becomes probably way too expensive for clinical care because these will be fairly rare events. There really were not very many failures. The drug works very well. But to understand more, you would have to see them when they pop up, not when the virus is already responding to having popped up, persisted and totally changed the population that you have now selected for an extended period of time. So, I don't know how much sooner you need to have it but that would require additional data to sort it out.

DR. PAXTON: Dr. Dee?

MS. DEE: You know, as far as clinical care

and cost, it wouldn't really be practical, I don't think, to do it once they failed. I think it would be better to find out what is going on before failure, or if there is something that we could use that would be helpful clinically to indicate whether you should stay on this drug or not. Now, what that time point is I am not really sure. I mean, is there anything we have seen today about time to failure that we could use to set a time point? Do you know what I mean?

DR. PAXTON: Does Pfizer want to address that?

DR. DUNNE: Yes, I think we can help a little bit with that question about monitoring for tropism switch along the way, and at least our position on what we think the value of a tropism is at the point of failure. Howie, do you want to do that?

DR. MAYER: I was going to specifically try to address the value of periodic tropism monitoring. Basically, I showed you in the main presentation that 60 percent of patients who were

on maraviroc BID achieved a viral load of less than 400 copies/mL and, therefore, a tropism test would not be possible because it is below the viral load where a tropism assay is normally done.

We also have data from the study showing that more than 50 percent of the patients who are treated with maraviroc by week 4 have no tropism result by virtue of the fact, again, that their viral loads, most of them, are too low to actually perform a tropism test. At week 24 there are few patients on maraviroc that have a tropism test. Approximately 40 percent of those are dual/mixed or X4 and about 60 percent are R5. So, what we have seen is that the emergence of dual/mixed or X4 is not necessarily a predictor of eventual virologic failure at week 24.

We have also conducted an analysis evaluating the timing of tropism change with the timing of virologic failure as defined by an HIV-1 RNA, and what we are seeing is that for 90 percent of the patients, or more, the timing of tropism switch occurs within 4-6 weeks of the timing of

failure by an HIV-1 RNA. So, the emergence of X4 does not appear to either be an absolute predictor of non-response or to help measurably in terms of the ability to determine when a virologic failure has occurred.

MS. DEE: But the thing of it is, I mean, that would be fine if maybe you would look at that in the postmarketing study in women and non-whites, that I hope you will do. Have I said that five times now? Anyway, you know, maybe you could look at the assay at different time points but what about in the real-life situations where people are going to have to pay for the cost of the test? You know, I just remember how hard it was initially when viral load testing became widely available and people didn't know how to read the results properly. I mean, what are people going to make of this in Peoria? No offense to anybody from Illinois!

DR. HAVENS: Excuse me, I live pretty close to Peoria so be careful about that.

But what we have been talking about here

is expanding these studies of looking at the tropism at, say, 24 weeks for people who still have detectable virus at a certain time point, and is that a predictor of later outcome in the same way that we are looking at further studies of C-trough as a predictor of later outcome in longer-term studies, and carrying through the studies that you are already doing. It sounds like you have already data from people who are detectable at 24 weeks and you will look at how that goes. So, the FDA should be very supportive of you doing those studies because that is a key issue to address which would help with the understanding of how to use this in clinical practice.

Now, to answer the question of what to do at failure, you already showed data of tropism switch at failure. For anybody who has been on the drug, had good control and then fails, the things you want to know are were they adherent, which you can talk about. That is free. Then you want to know are they resistant to the background regimen or are they resistant to the maraviroc. Both of

those cost money.

The federal guidelines recommend resistance testing in that context and this is just one more way to identify a virus that will or will not benefit from a certain kind of drug that you might or might not use. So, I would look at what you do at failure for anybody is to identify what drugs are available for use. In this context, if it is not CCR5 virus you won't benefit from maraviroc. You would have to look at the genotype or phenotype susceptibility because those are different than the tropism so that would have to be added to whatever susceptibility testing you are using to allow you to look at all those issues.

So, from a clinical perspective, the federal guidelines committees will need to look at recommendation of tropism testing both prior to using maraviroc and at the time of failure to identify what you would use in your next regimen.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: Just one other option, as we have discussed before, is that the dose is too low

even though people are compliant.

DR. PAXTON: We get back to the availability of that serum measure.

DR. HAVENS: I am glad somebody said that besides me.

DR. PAXTON: We keep coming back to it. Well, it seems kind of clear to me that we can't say you need to do it now, and all that, but the committee has offered up some useful things to think about as further studies are being designed.

Does anyone have anything further to add to this discussion before we move on to the last and final question? Last and finalB-that was a little bit redundant there! Obviously, it has been a long day.

Anyway, question number five was to please discuss the impact of the availability of maraviroc on the design of future Phase 3 trials for new antiretroviral agents in the treatment-experienced population and provide recommendations for how those trials should be designed accordingly. Anyone want to take this one on? Dr. Havens?

DR. HAVENS: Well, I think in a certain kind of way this trial is a good model for how to do it. Both in the FDA documents and Dr. Kuritzkes had a good slide showing the different in OBT. You made appropriate corrections for T20, whether that was in or out. So, I think the fact that we can sit here and suggest that the drug really works shows that this kind of adding to optimized background therapy is a reasonable study, and the kinds of data that were put together for this seem to have allowed us to make reasonable decisions towards approval.

DR. PAXTON: Anyone wish to add anything further to that? Dr. Birnkrant?

DR. BIRNKRANT: I think one of our concerns in raising this question was that the optimized background is becoming very optimized. So, is there a point where we go back to substitution studies? If there is another CCR5 that is being developed, should we look at a design where that would go up against maraviroc as well as, I guess, the optimized background, etc.? In other words,

the concern is we may not see a treatment effect with the optimized background. I mean, it is great to be in that position because that means we have more available drugs.

DR. HAVENS: Right, you would have to look at the effect of makingB-that would dramatically make it much more difficult to do the next study. So, if you change the rules now for doing a study on OBT, you know, addition to OBT, you really make the next study more difficult. You can see that if three drugs in OBT is no good so you could argue, okay, that is a regimen; don't add to that. But, short of that, I think you would be changing the rules in a way that would maybe make it harder to compare even. I am glad you are at the FDA.

DR. PAXTON: Dr. Dee?

MS. DEE: You know, I am wondering if this drug is approved and maybe the next drug that comes down the pike is approved, I mean, you are going to have to optimize the background regimen, I think, to compare other things to. So, I think we are in a better position mainly than we have been in for a

long time, and probably a more difficult position for a new drug to come up against. But, I mean, this would be helpful for the optimized background regimen. You don't think that is correct? I mean, plus, it is not cross-resistant to T20.

DR. HAVENS: Right, it helps the optimized background but then the question is for the next drug you want to use how are you going to really evaluate the drug? That is why I am so crabby about this kinetics thing because the kinetics are getting a free ride from the tipranavir and that is an issue with this drug and what we just voted on. The 300 BID looks better than it should because of the efficacy of the OBT. So, it is my personal, privately held opinion that the reason that the low kinetics looks good here is not because low kinetics is good for you but because it has good OBT. That is why this is such a key question. But it is tricky. I mean, tipranavir is a good background. There was some good background. You can't argue with the clinical data; I am not trying to argue with the clinical data, but I am just

saying that at 48 or 96 weeks we might see something different given back kinetics, and that is trickier to find. So, you have to demand a longer-term follow-up to be able to see how clear the kinetics issue finally sorts out.

MS. DEE: I love longer-term follow-up.

DR. HAVENS: But I have patients I want to start on the drug soon so, you know, it is a different issue. I mean, it is a balance that is very difficult to find and I think the more good drugs that people can put in an OBT, the harder it is to be highly critical, but I think this has actually gone very well and you get to see the signal here.

MS. DEE: I am wondering though, now that I re-read this question, are there going to be enough treatment-experienced patients to do clinical trials in the future. In other words, isn't that what you are getting at here? In other words, that we have enough peopleB-in other words, will the N be large enough in the treatment-experienced population to do this like we are doing them now

instead of having to deal with naive people first?

DR. BIRNKRANT: I guess that is partly related to it but I was really going for not that there wouldn't be enough patients because, unfortunately, I think there will be.

DR. PAXTON: I think I am kind of hearing that no one has jumped up to say, well, this is the trial design that we would recommend you do, that we are actually painting ourselves into a good corner, you know, of having more drugs available but it is going to, or necessity, going to complicate any further trials that we do. I think it is something we are just going to have to accept. It is not just in this realm. We are seeing it in prevention, HIV prevention; we are seeing it in all sorts of things. So, I don't really know that there is much more that we have offered in addition to that but we will think about it and if we come up with something we will email you. Dr. Yarchoan?

DR. YARCHOAN: I guess a special case is if there is a next CCR5 inhibitor and the question is,

is there any rational to use them together or, really, should they be compared against each other and I don't have an answer to that. But perhaps if there are some small studies using them together you will get some preliminary data.

DR. PAXTON: Well, I just want to point out that, unless there is anyone burning to answer, it is 4:20 so I apologize, we are 20 minutes over. But I wanted to thank everyone for their cogent, their wonderful comments and for your participation in this committee meeting. Thank you very much.

[Whereupon, at 4:20 p.m., the proceedings were adjourned.]

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