[Slide]

As you can see in the slide, we present the primary efficacy endpoint data for the two pivotal trials, studies 1027 and 10028. The primary efficacy endpoint was the mean change from baseline to week 24 in HIV viral load. You can see here the raw mean data for each of the treatment arms. You can see that for the QD arm it was 1.8 log reduction, for the BID arm, minus 1.9, and there was reduction in the placebo as well. Here is the adjusted mean. Adjustment was made for covariates of Fuzeon use as well as viral load greater than or less than 100,000. So, you see the adjusted means here, and this is the estimated treatment effect, so essentially subtracting what was seen in the placebo from the QD arm and placebo from the BID arms. So, these are estimates, for the QD arm minus 0.9 log reduction and for the BID arm nearly a 1 log drop. Essentially, our assessments of the primary endpoint duplicate those of the applicant. You can see here the 99.95 percent confidence intervals do exclude zero for

both the QD and BID arms.

[Slide]

For the primary efficacy analyses we did a number of sensitivity analyses and looked at both on and off treatment viral load data. You can see here these are the estimated treatment effects. We looked at completers through week 24 so those are people who had final observation through week 24 for this data set. You can see here approximately a 0.5 log reduction, as well as imputation of single values for those that were missing.

Our findings are that the results are similar to the sponsor sensitivity analyses. You can see here estimated treatment effects and all of the sensitivity analyses do support the superiority of maraviroc over placebo.

[Slide]

We also looked at essentially undetectable proportion of subjects with viral load less than 50 copies/mL at week 24. You can see here, this presents by treatment arm initially all subjects and you can see there was 44 versus 45 percent of

individuals in the maraviroc arms that were undetectable versus 23 in placebo. We looked at different characteristics, male versus female. You can see here what appears to be certainly preserved treatment effect across gender and, clearly, that there is a benefit, regardless of gender, over placebo. As was mentioned, approximately 90 percent of the trial was male so we have far less data on women really in both pivotal trials.

[Slide]

This looks at treatment effect based on gender and race. You can see here Caucasian versus Black. You can see that there was a pretty similar treatment effect, 46 and 48 percent, in Caucasians and this was clearly superior to placebo. If you compare Caucasian to Black, there was apparently a slight decrease in efficacy but there were very few African Americans in the trial so the certainty of that is unclear. I should note that even though there was a reduction compared to Caucasians, it was superior to placebo. Other races were at such low proportions that they were not separately

analyzed.

This looks at disease characteristics and, once again, we are looking at proportion of subjects with viral load less than 50 at 24 weeks. What I chose to do is look at viral load by quartile, which I think is a helpful way to see whether or not there is a difference, and I think you can appreciate that as you proceed from quartiles there is an increase in observed efficacy in patients who have lower and lower viral loads at baseline. This is true really in both groups from QD and BID and there is superiority across each viral load quartile to placebo.

One interesting thing worth noting is that even though in the lowest quartile group efficacy does appear quite similar in the two maraviroc arms, as you proceed certainly to the highest quartile you may be seeing an improvement in efficacy with BID, 31 percent versus 24 percent.

Next going to CD4 count, once again I looked at this by quartiles and I think you can appreciate that as you proceed across quartiles to

higher and higher CD4 counts, once again, there is evidence of a trend. For each quartile CD4 there is superiority over placebo and, once again, I think it was also noted by the applicant that if you do look at, say, the lowest quartile there is apparent benefit in the BID arm over the QD arm, 12 percent proportion that were undetectable in QD versus 21 percent in the BID arm.

Looking at the OSS score, which is this overall sensitivity score, basically it is looking at number of drugs that one is sensitive to so if it is zero you are essentially not sensitive to any drug, then proceeding to greater than or equal to 3, you can see that as one becomes sensitive to more and more alternative drugs there is an improvement in response, and this is true, of course, for placebo. Then, at this highest group, greater than or equal to 3 drugs being sensitive, you don't really see much of a treatment effect with maraviroc, which is perhaps not surprising as these individuals have multiple choices for reduction of viral load.

Also looking at Fuzeon use, yes versus no, at baseline, I think one would have to say it is difficult to say that there is any difference across maraviroc arms or any different in effect based on whether or not you were on Fuzeon at baseline, but important to note that once again, regardless of whether or not you are on Fuzeon, it was superior to placebo.

[Slide]

We also assessed change in CD4 count and you can see here this is a completers analysis through week 24. These are the mean changes, and this is once again just subtracting. You can see that there was evidence of CD4 improvement in the maraviroc arms. This is last observation carried forward at week 24. I will just repeat essentially what the applicant had said as well, that we do see in the low to high 50s benefit over placebo with respect to CD4 count at week 24. So, we do feel that the treatment effects are robust with respect to CD4 count.

[Slide]

As far as the conclusions for efficacy, we do find that the evidence of superiority over placebo is convincing. While the efficacy was reduced by the most conservative analyses, there remained at least 0.5 log reduction over placebo and we did see increases in CD4 cell count that were consistent.

The only group where there did not appear to be a benefit, and this is probably not surprising, is individuals with an overall sensitivity score greater than or equal to 3. These are people who have multiple treatment options for reduction of viral load.

[Slide]

What I would like to do now is find the safety data and I would like to just proceed to looking at FDA analyses of the safety data for maraviroc.

[Side]

My presentation will start with an overall summary of adverse events. I will proceed to mortality, malignancies, hepatic adverse events,

infection. We will look at additional adverse events and selected laboratory data.

[Slide]

This table shows really an accounting of all adverse events that occurred in studies 1027 and 1028 by treatment arm. As you would expect based on the randomization scheme, there are far more patients in the maraviroc arms. If you look at total adverse events, there is obviously going to be an increase in the maraviroc arms so an adjustment was made to look at average number of AEs per subject. You can see here that perhaps after adjusting by subject there may be an overall increase in maraviroc. But then, as you go down, grade 3/4 adverse events and average SAEs per subject, in fact if anything certainly for SAEs per subject, placebo is starting to increase.

Then a surprising thing happened. When we looked by 100 subject-years, so adjusting for not only the difference in total numbers of patients per arm but the differences in total exposure because, as was mentioned earlier today, patients

who were in the placebo arm actually had a shorter duration of time of monitoring, typically because they were failing virologically. So, the surprising thing is that in the placebo arm you see, in fact, more than a doubling of AEs per 100 subject-years and there is an increase in grade 3/4 adverse events, as well as SAEs per 100 subject-years. So, we went on an expedition to understand why this could be.

[Slide]

This looks at median treatment days so, as discussed previously, on average in the maraviroc arms you are talking about 230 days of observation versus 145 during the double-blind period in placebo.

[Slide]

So, this table shows days to individual AEs during the double-blind period. This is for the placebo arms for the two pivotal trials although it is actually somewhat similar to what happened in maraviroc as well. You can see that there is really an increase, certainly in the first

25 days, of adverse events. This is probably not surprising because what people are starting on, on day zero, is an optimized regimen so they are being exposed to a number of new drugs, not just study agent. One concern, of course, might be could this just simply reflect patients leaving the trial and I don't believe that that is the case.

[Slide]

This shows days to subject discontinuation from the double-blind period in the placebo arms and you can see here that patients are leaving early, but not many and, in fact, it is not until day 100 where a substantial number have left the trial.

So, the reason I have gone into all this is that all time is not equal during the trial and when you do a time adjustment analysis you are essentially, for placebo, enriching placebo arms with this period of time. So, you have a shorter period of observation. You have essentially an enrichment of what is essentially a more dangerous time during the trial. I don't want to say that

one cannot adjust for time but one should be cautious and understand that there is an issue because of the pretty marked disparity in time of observation in the arms.

[Slide]

I would like to proceed to the mortality data.

[Slide]

In this slide we see all mortality that occurred in really all 4 trials that have been mentioned. 1026 is a trial that is for treatment-naive patients. It is ongoing. You can see here that there was a 2:1 randomization so we don't see any evidence of imbalance in this trial.

In 1027, which is a 4:1 randomization, you can see the different diagnoses for cause of death and we don't see evidence of imbalance in 1027.

1028, the other pivotal trial, is a trial that certainly brought concern because, as you can see here in the treatment arm, it is all on maraviroc. So, this was, once again, a 4:1 randomization so it wouldn't take many events in

the placebo arm to have balance but you clearly see that there is not balance in this arm.

1029 was also looked at. I think this was mentioned earlier in the day, this is the dual- and mixed-tropic patients. This was a 2:1 randomization and you clearly do not see imbalance in this arm.

[Slide]

So, with respect to the mortality data, we do see a numerical increase in mortality in maraviroc but there are a number of things that I think bear consideration. The imbalance was seen in only one of four trials that are large in investigating maraviroc. The degree of imbalance is actually quite small. With the help of the statisticians, I did a p value calculation. You can see it is 0.6 and that represents a very small degree of imbalance in the overall events in maraviroc versus placebo. There was no clustering of death cases that you felt perhaps maraviroc was causing and you might have expected to see a certain pattern, but we did not see any pattern.

The types of deaths that were observed were consistent with the population that was studied.

It is also worth noting that this was a very sick population at baseline. There were 11 additional deaths that occurred during a roughly 6-week period between screening and randomization, so prior to ever receiving study agent.

[Slide]

I would like to go on to malignancies. This was, of course, a concern based on the mechanism of action. This is blocking receptor on immune cells so one might be concerned that there could be an increase in malignancy. There was also data that suggested the potential that there is an increase in lymphoma.

[Slide]

You see here all lymphomas diagnosed during studies 1027 and 1028. These are treatment. I should probably note that above this line is during the double-blind or active phase. Below the line is during an open-label phase. I think you can appreciate overall that, given the 4:1

randomization, we certainly don't see an increase in lymphoma over placebo.

[Slide]

We also assessed non-hematologic malignancies during the double-blind period. This is an accounting of all the malignancies that were listed in the adverse event database, once again looking by treatment arm. These are the totals. Certainly, there is no evidence of an increase once one takes into account the randomization scheme of 2:2:1.

[Slide]

Next going to hepatic adverse events, this was also of some concern given the experience with aplaviroc.

[Slide]

You see in this slide the hepatic AEs that occurred during trial, once again, pretty consistent, QD, BID, placebo. This looks at whether or not a subject at any time during the trial had a hepatic adverse event. You can see here that the numbers are actually fairly similar,

7 percent, 9 percent and 6 percent. So, I think it would be a tough call to try to say that there is a clear increase.

This column is time adjusted placebo. This was my way of trying to at least portray what one would have expected if you adjusted for both the increased duration of time and the increased numbers of patients in the maraviroc arms versus placebo so 34 if you adjust for both number of patients and really total time of observation, 34 compared to 39 and 30. It is a subtle different, if any. If you look at total numbers of AEs, the difference does become a bit more remarkable so 53 and 61 in the maraviroc arms versus 36. So, what is essentially happening is that for a roughly similar number of patients you are seeing a slightly increased number of adverse events.

If we go on to look at grade 3 and grade 4 adverse events in the maraviroc QD and BID arms versus time adjusted, you know, if you compare certainly BID you could say that there is an increase that is probably not striking if you look

at just SAEs, 2 and 9 in the maraviroc arms versus 2 in the placebo but if you adjust for time of observation it is 5. So, we are talking about pretty small numbers of events at this point and I don't think you could say that there is a clear increase in maraviroc for SAEs that are hepatic in nature.

[Slide]

Then we went on to look at individuals who had events that met Hy's law. Just to review, Hy's law has a number of factors to take into consideration. AST or ALT needs to be greater than or equal to 3 times the upper limit of normal, and there are discrepancies in Hy's law citations but what we commonly use is total bilirubin greater than or equal to 2 times the upper limit of normal. Others have been proposed but this is what is used in our analyses. There should be no marked increase in alkaline phosphatase. It can be elevated but it shouldn't be markedly elevated to suggest that there are possibly gallstone-induced alkaline phosphatase elevations. No evidence of

another cause. And, the importance of Hy's law is that it predicts 10-50 percent likelihood of death or need for liver transplant.

What we found was that we were not able to really assign any hepatic adverse event as meeting Hy's law. This was due to the criterion of requiring no evidence of another cause. These were very complicated patients at baseline from the hepatic standpoint. Approximately half of the individuals had liver enzyme abnormalities at baseline.

[Slide]

This is a case history, just to make the point or give you a sense of who these individuals are and how complicated they are. I won't read the whole thing to you but this was a 43 year-old woman. She had a history of injection drug use, alcoholism and hepatitis C. She received maraviroc for 203 days. She did not have evidence of hepatitis B but did have evidence of hepatitis C. She drank 5 alcoholic beverages per week. Her liver enzymes were elevated at 101 and 43 at

baseline. Her total bilirubin, while normal at baseline, had been elevated sometime prior to enrollment. Her bilirubin did rise during the trial. She had both direct and indirect elevations of bilirubin. She had also been on atazanovir prior to maraviroc but this was stopped. She had 3 reported liver AEs during the study, which included bilirubin on 2 occasions and hepatosplenomegaly once.

[Slide]

We also assessed liver enzyme abnormalities in studies 1027 and 1028. This shows all patients who had either an AST or ALT elevation above the upper limit of normal 3 times, 5 times and 10 times the upper limit of normal. Once again, you can see by treatment arm that if you look at the proportions, I think it is pretty clear that one is not able to say that there is any increase in the maraviroc arms as far as liver enzyme elevations over placebo.

[Slide]

We also assessed total bilirubin elevation

in a very similar manner. I think it is pretty clear, as you go looking at upper limit of normal versus multiples of increase over the upper limit of normal that there is no evidence of any increase in the maraviroc arms over placebo.

[Slide]

Next I would like to proceed to infectious adverse events. Again, this was another topic that has been of concern in development of the CCR5 inhibitors. It is blocking a receptor on immune cells so one might be concerned that there might be an increase in infectious events in individuals receiving maraviroc.

[Slide]

What you see here are the most common infection-related adverse events during the double-blind period. These are numbers of AEs, not numbers of subjects, looking at QD, BID and placebo. This is my time adjusted, which is simply placebo times 2.6. If you look at upper respiratory tract infection as simply a medDRA term in the data set, I think you would say that if you

adjust for time there is no evidence of an increase.

Interestingly, there are multiple ways of describing a cold so if you combine all the terms that might be consistent with cold--so nasal pharyngitis, nasal congestion, rhinorrhea--you do see what could potentially be an increase in upper respiratory tract infection. What we saw is for the QD arm a rate of 31 percent, BID arm 35 percent, and in placebo 21 percent which doesn't adjust for time, meaning that even if you do make a correction for time there is a slight increase in upper respiratory tract infection.

Again, these are AEs, not numbers of subjects, and here you see an increase in the QD arm in candida infections but, interestingly, not in the BID arm. So, I would have to say that although it is important for people to know that this increase was observed, it is a complicated thing. You might have expected either the same or an increase in the higher dose arm and we don't have that.

For herpes number of events, and this is time correction, you do see what appears to be an increase in the BID arm. Lastly, for influenza you can see 19 versus 7 and 1 in the placebo arm if you round time adjustment of 3 for placebo. So, there is clearly an increase although, once again, it is in the QD arm and is certainly less apparent in the BID arm, which makes for a complicated way to explain this. These are just events. If you look by patient, there are 18 patients with 19 events in the QD arm; 7 patients with 7 AEs in the BID arm and 1 in the placebo. I would like to go into the candida and herpes events in a moment.

[Slide]

These are the category C events during the double-blind period. We do not think that there was an overall increase in category C events or in infections overall in the maraviroc arms. These are, once again, numbers of AEs in the two pivotal trials. In the QD arm you do see an increase in total numbers of AEs for candidiasis even over the time-adjusted placebo. The same is true for herpes

virus infection. For the other events, certainly if anything, if you do time adjustment placebo looks better. So, once again, it is really the candidiasis and herpes infection categories where there may be evidence of increase.

[Slide]

Getting into a bit more of the hepatic infections during the 2 pivotal trials, there were 65 AEs total. You see here the breakdown by treatment group, 25 AEs in 18 subjects in the QD arm, 32 AEs in 29 subjects in the BID arm and 8 and 8 in the placebo arm. So here, if you look at just total AEs for hepatic infection, the BID arm does look a bit worse and does not correct for time. So, even if you adjust the placebo arm the BID arm remains elevated over placebo for hepatic events.

We also looked at the herpes-related adverse events that qualify as a category C event. There are far fewer events. I think it does make it somewhat difficult to interpret. Interestingly, the proportion of individuals having such events is actually higher in the QD arm, not in the BID arm.

So, I think it is going to be hard to really pull this altogether and part of that I think is just because of the fewer events in the category C herpes-related AEs.

[Slide]

The purpose of this slide is to show you what were these herpes events, as best as can be defined in the adverse event database. For the most part, events were termed as herpes simplex. That was the most common. Also herpes virus. You can see here other locations that were provided in the AE data set. It does get to be very hard to compare once you break down herpes events into these multiple categories so I don't know that one wants to make direct comparisons between either placebo or placebo time adjusted. But this just shows you where the events are coming from.

[Slide]

With respect to candidiasis infections during the double-blind period, you see here that there were 70 candidiasis adverse events once again broken by arm, QD, BID and placebo. Here you see

in the QD arm a fairly marked increase in total AEs but really not in the total number of subjects. So, I would describe this as being complicated. I do think, once again, it is something that the committee should know and the public, but I don't think there is going to be an easy interpretation. You know, if there is an increase associated with maraviroc I think the overall assessment might be that it is subtle.

This looks at the category C candidiasis adverse events. Once again, we are talking about a fairly small number of patients who had such events. Actually, there were 19 adverse events and these are the total numbers of patients who had such events. I think because of the small number of events it is hard to interpret in any convincing way.

[Slide]

This slide once again is really intended to show you what types of candidiasis events we are talking about. Predominantly it was oral candidiasis and esophageal candidiasis that were

far and away the most common. It does allow for direct comparison for both placebo and time-adjusted placebo but when you divide type of events, such as candidiasis, in multiple ways you do get very small numbers and it does make it difficult to make direct comparisons of maraviroc versus placebo.

[Slide]

Moving on to additional adverse events that were assessed during the trial, or during our analyses.

[Slide]

Cardiovascular adverse events were assessed, both because they are important and due to the concern of postural hypotension and that maybe that could have predisposed people to have cardiac events. What you see here is treatment group. It is all in the maraviroc arm. So, each maraviroc term represents a single patient. It is perhaps a slightly complicated slide because what you have is that a single patient can have more than one adverse event. So, this is the way that I

chose to present. So, this patient had 2 adverse events, although, you know, tightly linked in time. This patient had 3 adverse events, all cardiac in nature.

The thing to point out I think in this slide is that all events were in the maraviroc arms. The patients themselvesB-if you look at their medical history, other than 2, this one and this one, they all had either a diagnosis of cardiac disease or strong risk factors for cardiac disease. Even individuals who didn't might be, on the basis of gender and age, considered at risk.

Here you see the actual adverse events that occurred. These were all ischemic events. You can see here the days from starting maraviroc to the event and we don't see a particular pattern, other than that they occurred well after starting maraviroc.

[Slide]

So, this obviously raised some concern in our minds, seeing only events in maraviroc. So, we did look if there was an imbalance in cardiac

disorders at baseline. There were 95 patients who had a cardiovascular disorder diagnosed at baseline, QD, BID and placebo arms. You do see a slight increase in the QD and BID maraviroc arms over placebo so that is present. Then, if you go to looking at just ischemic cardiac disorders, once again you see a very slight imbalance, 5 percent in the QD arm versus 4 in the BID arm and 3 percent in placebo. But I would have to say that at this point we wouldn't be reassured, based on this degree of imbalance, that we would expect to see all events in the maraviroc arms.

[Slide]

Another assessment was done. Because of this imbalance in ischemic events, we wondered whether or not there was an increase in overall thrombotic events. This is numbers of subjects with an adverse event in the 3 arms, QD, BIT and placebo. I think you can compare across all of these different categories and here are the total numbers of these thrombotic events. Certainly, even just adjusting for the numbers of patients in

each arm without even adjusting for time, you can see that there was an increase in thrombotic events based on this type of analysis.

[Slide]

Postural hypotension has been a concern for this drug. As was mentioned earlier in the day, this was a dose-limiting adverse event at doses actually higher than assessed in the pivotal trials. We performed a search looking at different terms--hypotension, orthostatic hypotension, dizziness, syncope-Blooking to see whether or not, if you combined all these terms are we seeing imbalance in maraviroc. I think what is fairly clear here is that the answer is no. In the QD arm there was 12 percent versus 9 percent in BID and 9 percent placebo. The QD armB-it is really hard to understand, but we are talking about relatively small numbers of patients. If you adjust for time you get into a very similar event rate for placebo and maraviroc if you multiply by 2.6. So, what I would say is that overall there really is no evidence of an increase in adverse events that one

might attribute to postural hypotension during the 2 Phase 3 trials.

[Slide]

So, AEs that were potentially associated with QT prolongation were assessed. As I think was mentioned earlier, the preclinical testing revealed a potential for QT prolongation with maraviroc, although this was at doses 6-12 times that were assessed during the pivotal trials. A previous CCR5 antagonist was found to cause QT prolongation so that was another reason that we had some concern.

A thorough QT study for maraviroc was determined to not be adequate by FDA. While there was no significant prolongation with maraviroc, the control arm was not felt to be interpretable because it essentially didn't decrease in the manner that we anticipated. So, at this point attempts are underway to resolve this issue with the applicant.

Perhaps reassuringly, an assessment was performed using multiple medDRA terms that could be

associated with ventricular arrhythmia. There were no AEs specifically mentioning ventricular arrhythmia during the 2 Phase 3 trials. If you look here, you can clearly see that there was no imbalance or no increase in maraviroc versus placebo for these potential ventricular events.

[Slide]

Another assessment was performed looking at CPK elevation. These were the terms that were used, basically CPD increase, myositis, rhabdomyolysis. There were 19 subjects with such a preferred term. You can see in the maraviroc arms 1.7 percent in the QD arm, 2.6 percent in the BID arm and in placebo 0.5 percent. So, there does appear to be an increase and one could even say potentially a dose response. We are seeing more in the BID arm. If you do an adjustment for time it is fairly straightforward, it is 2.6. So, both these numbers are certainly above 2.6, although relatively few number of events.

[Slide]

We went on to look at CPK elevation during

the trials and this is multiples of elevation above baseline abnormal, 2 times, 5 times and 10 times. You can see what looks to be an increase in the maraviroc arms for being abnormal, 55 percent versus 44 percent. This appears to continue at 2 times the upper limit of normal, 29 and 28 percent versus 20, and basically disappears as you go to 5 and 10 times the upper limit of normal. So, there does appear to be an increase in modest elevations in CPK.

[Slide]

Lipids were assessed. You can see here QD, BID and placebo. What we looked at was 15, 30 and 50 percent increases above baseline. You can see here 39 percent and 38 percent versus 24 percent in placebo, 23 and 22 versus 20, 12 and 9 versus 3. So, there does appear to be an increase in lipids in the maraviroc arms.

[Slide]

A concern was raised that while the maraviroc arms are in the trial longer so they are on average going to be exposed to protease

inhibitors for a longer period of time, maybe that could be a reason for an increase in lipids in those arms. So, what was performed was looking at fasting total cholesterol at week 24, plus/minus 2 weeks, during the 2 pivotal trials. So, this is really a completers analysis. You can see that the denominators change. These are the numbers of patients who had a lipid level at week 24, plus/minus 2 weeks of week 24. I think what you can appreciate is, once again looking at 15, 30 and 50 percent above baseline, 45 and 43 percent in the maraviroc arms versus 31 percent in placebo, 26 and 25 percent at 30 percent elevation above baseline versus 14 in placebo, and 13 and 9 percent had elevations more than 50 percent above baseline versus 5 in placebo.

Then, if you assess by more standard measures that have been used to look at cholesterol so individuals greater than or equal to 200 versus greater than or equal to 240, you can see what perhaps is a very slight increase in the maraviroc arms, 24 and 22 versus 20, you know, once again,

not really seeing a dose response which might undermine the finding. And, with greater than or equal to 240 you see that there was potentially an increase in the BID arm of 16 percent versus 11 and 11 in the placebo and QD arms.

[Slide]

Moving on to LDL cholesterol, once again I looked at 15, 30 and 50 percent above baseline in the 3 arms, and you can see that there was 31 and 29 percent of individuals in the maraviroc arms with a 15 percent elevation versus 22 in placebo; 21 and 18 in the maraviroc arms versus 14 in placebo for 30 percent elevation; and at 50 percent elevation 13 and 10 percent in the maraviroc arms versus 7 in the placebo. So, this is a pretty sensitive analysis I think to see whether or not LDL is increasing.

[Slide]

But then if we look at what one might call meaningful increases in LDL and these are more standard ranges to look at LDL, 21 and 22 versus 23 greater than 100; greater than 130, 11 and 14 and

12. Then, if you go to the higher increases in LDL, really you are not seeing any increase I think overall in individuals meeting these important benchmarks of LDL elevation in the maraviroc arms. It looks fairly similar to placebo.

[Slide]

So, in summary, the FDA analyses have not revealed an increase in mortality or malignancy overall in association with maraviroc. We don't see any clear evidence of hepatotoxicity, but we would like to emphasize that this was a complicated patient population and there was a high rate of liver abnormalities at baseline.

With respect to infections, we don't see an increase in infections overall or in category C types of infections. However, there was a possible increase in candida and herpes and influenza infections.

There was a possible increase in cardiac ischemic events which we don't think is explained by any background increase in cardiac diagnoses in the maraviroc arms. I think one thing to note is

that we are obviously continuing to review all cases as they come in and we will have 48-week data to also try to understand whether or not this is a pattern that continues. There is a possible increase in myositis and what I would describe as a mild increase in total cholesterol and LDL levels.

Thank you very much for your time. What I would like to do now is introduce Dr. Pravin Jadhav who will be presenting pharmacology data.

Exposure-Response Modeling

DR. JADHAV: Thank you, Dr. Proestel. Good morning, everyone.

[Slide]

On behalf of the clinical and pharmacologic review team, I will be presenting an exposure-response analysis relating maraviroc drug concentration that is C_{min} and the probability of virologic success as defined as RNA less than 400 copies/mL.

[Slide]

Our major aim to review and extend the sponsor's analysis was to assess the

appropriateness of the proposed dosing regimen of the BID versus the QD regimen. As you have heard in the morning from Pfizer's presentation, there are differences in some secondary and key secondary endpoints on BID versus QD dosing. I will comment based on the exposure-response analysis. We were also interested in assessing the utility of C_{min} virologic success relationship to maximize success in every patient that will be treated with maraviroc.

[Slide]

I have two key points to deliver from this presentation today. First, that the probability of virologic success is concentration dependent, meaning the maximum success is achieved at concentrations somewhere in the region of greater than 50-75 ng/mL. For this presentation I will focus on a threshold of 75 ng/mL.

In addition to C_{min} we find that there are other important predictors of success such as CD4 count, viral load, OSS and baseline tropism. Based on the relationship that we have developed, the

proposed BID dosing seems reasonable as the BID dosing will ensure 60 percent of patients to be above 75 ng/mL compared to the QD dosing which is about 18 percent.

Secondly, we find that maraviroc concentrations could be important to explain the lack of response in certain patients, to assess compliance and assess any need for dose adjustment to maximize the success. Our simulations indicate that if we were to target patients with C_{min} less than 75 ng/mL the probability of success can be increased to 62 percent from 56 percent which will be achieved with the current dosing. However, at the population level the probability increases from 67 to 69 percent. I will go into details of these numbers and how those were derived.

As I am presenting you this analysis to be thinking of ways we can use to maximize patient success. As you heard in the morning, one of the aims of antiretroviral treatment is for optimum full viral suppression in each patient.

[Slide]

We used data from 2 pivotal studies, 1027 and 1028. Out of 1,049 patients that were treated with maraviroc or placebo, 76 patients were excluded due to missing covariate information so our effective sample size was 973 subjects. C_{min} was used as an exposure variable and the endpoint that we used as one of the key secondary endpoints was RNA less than 400 copies/mL to define virologic success. We also used important factors that are known to affect the virologic success in the analysis.

[Slide]

So, the first question we had was is the virologic success concentration dependent on maraviroc C_{min}?

[Slide]

What you are looking at is the proportion of patients with virologic success defined as 400 copies/mL or less by plasma trough concentrations, the median plasma trough concentrations. The maraviroc-treated patients are divided into quartiles so these are the four points from the

patients who were treated with maraviroc. You will see that when people were treated with placebo and the optimized background the current probability of success, the proportion, is about 30 percent. As the median concentration of maraviroc increases to about 20 ng/mL the probability of success increases to 55 percent. For further increases, that is, to 40 ng/mL median, the probability of success increases to a little over 60 percent. So, clearly, there is a concentration-dependent relationship for probability of success for maraviroc. We also looked at other endpoints, such as less than 50 RNA copies/mL, protocol defined failure and at least 1 log drop at week 4 and we found a very consistent relationship, as is shown in the graph here.

[Slide]

When we model the relationship we find that, in addition to C_{min}, there are other important predictors of success. You have seen in 2 presentations in the morning that the success differed based on the CD4 count, viral load, OSS

and other factors. Based on the mechanistic basis, as the CD4 count is higher if the virologic baseline viral load is low the probability of success is higher in patients, and there are other predictors of the success that were found that are important from the patient benefit viewpoint.

[Slide]

So, I am going to zoom back to the relationship of probability of success and concentration. We will see that somewhere in the region of 50-75 ng/mL maximum success is achieved and further increases in concentration offer minimal additional benefit. Surely, the threshold I am quoting here, 50-75 ng/mL, is rather subjective but the point I am trying to make here is that irrespective of the threshold, from the patient's benefit viewpoint you will rather have patients in the higher concentration range, that is, the threshold of 75 or 50 ng/mL, than having a patient in the lower concentration range. So, we were interested in understanding what are the factors that will affect the patients who are in

the lower concentration range, and is the dosing supported based on the C_{min}-virologic relationship.

[Slide]

When we look at the distribution of plasma concentrations by the dose groups that were employed in the pivotal trial, you will see that with 150 mg BID the concentrations were higher than with the 150 mg QD dosing, as was the same case with 300 mg BID versus 300 mg QD. The doses were different based on the optimized background.

You will see that about 60 percent of patients are above 75 ng/mL, which is the blue dotted line that is shown here, with the BID dosing compared to 18 percent on the QD dosing. So, just by selecting a good dose, that is, BID regimen compared to the QD dosing, it does ensure most patients are above 75 ng/mL.

[Slide]

However, there is still a considerable number of patients who are below 75 ng/mL and we were interested in understanding what are the important predictors that could affect the lower

C_{min}. Can we identify the characteristics of patients who will consistently be lower in their concentration ranges?

[Slide]

So, let me get back to the distribution that I showed you only for the 150 BID and 300 BID, with 150 BID as administered with the PI and 300 BID without the PI. As you will see, the number of patients on the 150 BID obviously is higher, 300 or so patients versus 90 patients on 300 mg BID. The concentration range is rather wide. Somewhere between 0 and 500 ng/mL concentrations are achieved with the current dosing. And, with 150 mg BID there is about 28 percent of patients who are below 75 ng/mL, as is shown by the dotted blue line here. The red line represents the median concentration. With respect to 300 mg BID, the percent of people who will be below 75 ng/mL is higher, that is, about 77 percent of patients out of 88 patients.

[Slide]

So, we looked at the factors that will lead to have patients consistently in the lower

concentration range because, as I told you in the previous slide, we would have patients in the higher concentration range than having them in the lower concentration range. We looked at several extrinsic and intrinsic factors that could explain the variability in C_{min}. Here is the distribution of C_{min} by the optimized background therapy with different drugs, and I am showing you very few selected drugs.

As expected, the CYP3A4 inducer in efavirenz and nevirapine, they do exhibit slightly lower concentration compared to the other groups and we also selected other PIs that we expected to have different degree of inhibition. As you see, fosamprenavir has a different degree of inhibition than saquinavir. However, the aim of this analysis was to find out a factor or a combination of factors that would consistently lead us to concentration less than 75 ng/mL, which is shown by the dotted line here.

But the interpretation of this graph is rather complicated because, remember, a particular

patient will have several drugs on board so one patient could be represented at several instances in this graph. But even then, we cannot identify a factor that could give us consistently 75 ng/mL. Also, we looked at race and other factors. As you see with race, the majority of the population was Caucasian and the data were limited on other races to make any interpretation of factors leading to concentrations less than 75 ng/mL.

[Slide]

Having said that, we were interested now in how can we better utilize the C_{min} virologic relationship that we established to maximize success in patients with C_{min} less than 75 ng/mL.

[Slide]

As we have learned from my presentation and also from the previous presentations, there is a combination of factors that are important for success, and there is a combination of factors that could lead to lower C_{min}. There are factors such as compliance. Drugs that are tested or not tested in clinical trials become more important in actual

clinical practice to offer the success that is shown or the benefit that is shown in the controlled trial.

On that note, we think that the concentrations of maraviroc could be important to assess lack of response in certain patients because it may be due to poor compliance or it may be due to some patient-related factors that might need dose adjustment. So, to answer that question we performed simulations by evaluating one of the strategies that could be used to maximize the success.

[Slide]

I am going to show you one strategy that is doubling of the dose if C_{min} is lower than the defined threshold. The simulations here use data from 399 patients that were treated with 350 BID. The QD regimen was not included in this analysis. And, it did account for doubling of doses, that is, the current regimen is 300 mg BID but if administered with efavirenz or nevirapine in absence of PI the doses were increased to 600 mg

BID. Then we used a certain threshold, and I evaluated about 5 thresholds, ranging from 10-100 ng/mL.

So, for a patient who was, say, on 300 mg BID and was below 10 ng/mL, a 600 mg dose was administered to see what kind of new response rate will be obtained if we double the dose in only those patients who are below a certain threshold. Note that only one dose doubling was allowed so we are capping the maximum dose to 300 BID with 600 mg BID without the PI.

[Slide]

Here are the results from the simulations. What you are looking at is the new probability of success that is, again, defined as less than 400 copies/mL. With the current dosing the probability of success is about 67 percent. If we double the dose in patients who are less than 10 ng/mL the probability of success increases slightly, about 67 percent, but note that the number of patients who are below 10 ng/mL is lower. At 75 ng/mL, that is, if we double the dose in patients with 75 ng/mL, we

find that the probability is about 69 percent.

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Now let me zoom on to the patients who got double the dose at 75 ng/mL. In this exercise we used 399 patients. Of these 399 patients, we find that 146 patients had concentrations less than 75 ng/mL. As you would expect from the concentration-response relationship, the overall probably will be only in those 146 subjectsB-was 46 percent. That is expected with the current dosing. When we double the dose the probability increases to 62 percent. However, at the population level, because the actual sample size was 399 patients, the probability only translates to about 2 percent.

[Slide]

So, having said that, while we are interpreting in two ways for looking at the same numbers, 2 percent and 6 percent, let me give you a little perspective or practical aspects of individualized dosing. Without a doubt, we need knowledge of the concentration-response relationship and when we evaluate a dose doubling

strategy we find that patients who are in the tail ends of the distribution, that is, less than, say, 25 or 10 ng/mL, one does doubling will not allow us to get to 75 ng/mL so we are limited by dose doubling, and because those patients might need multiple dose adjustments, our safety experience at higher doses is limited.

Also, the success is multifactorial. We also need knowledge of other factors, as you will hear from our next speaker, that the probability of success is dependent on OSS, baseline tropism and viral load. So, in addition to concentration, if you need to maximize the success in individual patients when we treat them, we need knowledge of other factors.

At this time let me also acknowledge help from our Pfizer colleagues to finalize this analysis and quickly getting back to us.

[Slide]

So, in the end I hope I have convinced you that the probability of virologic success is dependent on maraviroc concentration, and somewhere

in the region of 50-75 ng/mL we have a better chance of success. We also find, and you will hear more about it in the next presentation, that in addition to C_{min} the probability of success is influenced by several other factors that are important. And, with the proposed dosing we find it a reasonable choice that most patients, about 60 percent of patients, will be above 75 ng/mL compared to the QD dosing. Finally, we also find that concentrations are important to explain lack of response in certain patients because it might be associated with compliance or some factors that are tested or not tested in the clinical trial to achieve success equivalent to what is shown in clinical trials, and might need dose adjustment in certain cases. With simulations, we have shown that the probability of success could be increased to 62 percent from 56 percent in patients with concentrations less than 75 ng/mL. At the population level the probability would translate to 2 percent.

With that, thank you very much for your

attention and I would like to welcome our next speaker, Dr. Lisa Naeger to give a talk on tropism and resistance.

Tropism and Resistance

DR. NAEGER: Thank you, Dr. Jadhav.

[Slide]

I will be discussing the resistance and tropism analysis of maraviroc.

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As mentioned earlier, maraviroc has a novel target. It targets a host receptor, the CCR5 receptor, rather than a viral target. As such, it has unique resistance issues. Resistance to maraviroc can occur in a classical sense where the phenotype changes by virus mutation resulting in viral entry and replication in the presence of the drug. However, since this drug targets the CCR5 receptor and will mechanistically work against only CCR5-tropic virus the virus can bypass maraviroc by a tropism switch of the virus to use the X4 co-receptor or outgrowth of an already existing X4 virus.

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Our analysis examined both changes in tropism and genotypic and phenotypic changes as mechanisms of viral resistance to maraviroc. In the baseline analyses of studies 1027 and 1028 the genotypic and phenotypic susceptibility scores were used to determine susceptibility to the optimized background therapy. A score of 1 was given for each susceptible drug in the optimized background. Therefore, the higher the genotypic and phenotypic susceptibility score, the more susceptible drugs were available in the optimized background therapy.

The genotypic and phenotypic susceptibility scores were balanced across the 3 treatment groups in both studies, with the median GSS score of 1 and a median PSS score of 2, and 67 percent of the subjects had an overall susceptibility score of less than or equal to 2, meaning they had 2 or less active drugs in their optimized background therapy; 30 percent had one potentially active drug in their optimized background; and 14 percent had no potentially

active drug in their optimized background. This is consistent with the heavily treatment-experienced population.

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Looking at tropism at baseline, 2,560 subjects were screened and 56 percent were found to have CCR5-tropic virus. About 10 percent of the viruses changed from R5-tropic to dual/mixed or were non-phenotypable by the assay in the time period from screening to baseline. So, about 90 percent of the subjects enrolled had CCR5-tropic virus at baseline.

I would like to note that throughout these trials it appears that the percentage of isolates which were non-phenotypable using the Monogram tropism assay ranged from 5-15 percent.

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So, one of our main questions was why did the subjects fail maraviroc treatment in studies 1027 and 1028. Reasons for failures could include co-receptor switch from CCR5-tropic to CXCR4-tropic virus by mutation of the virus, or outgrowth of

CCR5-tropic viruses that are resistant to maraviroc, or outgrowth of X4-tropic viruses that were present at baseline but not detected in the Monogram standard tropism assay. One of the limitations of the Monogram assay is that it is not able to detect with 100 percent sensitivity X4 virus when present below 10 percent levels in a viral mixture. Another reason for failure could be resistance to the optimized background therapy and, in addition, the host CCR5 genotype might also contribute. Although not known at this point, it might be possible that maraviroc may not bind efficiently to some host CCR5 receptor genotypes.

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For resistance analyses we used as-treated analyses. Therefore, subjects are censored from the analysis if they discontinued while suppressed, with less than 400 copies, or if they discontinued with greater than 400 copies early, between baseline and week 4, or if they discontinued between baseline and week 8 with at least a 0.5 log decrease and no rebound. Forty-nine and 39

subjects were censored from studies 1027 and 1028 respectively, giving a total of 88 that were censored.

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Using the censored data set, we first determined the percentage of virologic failures that had either a CCR5-tropic or CSCR4-tropic virus at the time of failure.

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This analysis was done using two definitions of treatment failure, the protocol defined treatment failure definition and subjects with the protocol defined definition, as well as subjects that had greater than 400 copies at week 24. Regardless of the definition of treatment failure, many subjects failed with CXCR4- or dual-tropic virus in the maraviroc arms compared to greater than 80 percent of the subjects in the placebo arm that failed with CCR5-tropic virus. A high percentage of treatment failure on maraviroc appears to be driven by tropism change from CCR5-tropic to CXCR4- or dual/mixed-tropic virus.

This supports the mechanism of action of maraviroc, and suggests emergence of X4-tropic virus is a prominent reason for failure on maraviroc.

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As I mentioned earlier, another reason for treatment failure could be resistance to the other drugs in the optimized background therapy. Most subjects typically had low phenotypic and genotypic susceptibility scores at screening, indicating reduced susceptibility to their optimized background therapy.

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Overall in both studies, as the number of susceptible drugs in the optimized background increased, reflected in an increased overall susceptibility score, the percent of subjects that achieved less than 400 copies increased in the maraviroc arms, shown in yellow and blue, and it increased to 70 percent if there were 3 or more susceptible drugs in the optimized background. In the placebo arm, shown in red, response rates were less than 20 percent if there were less than 2

active drugs in the optimized background and increased to 21 percent when subjects had 3 or more susceptible drugs in their optimized background.

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When examining the optimized background therapy in subjects who were treatment failures, 28 percent of treatment failure subjects had no susceptible drugs at baseline and there was no difference between the arms. When looking at changes in susceptibility to optimized background drugs on therapy, 43 percent of treatment failure subjects lost susceptibility to drugs in their optimized background while on treatment. Again, there was no difference between the arms.

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Looking specifically at enfurvitide use, enfurvitide use in failures was comparable between arms at 45 percent. About 70 percent of the subjects developed enfurvitide resistant mutations on treatment on the maraviroc QD arm and placebo. There were significantly fewer enfurvitide mutations that developed on enfurvitide treatment

in the maraviroc BID arm, with 52 percent compared to the QD and placebo arms.

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Examination of overall susceptibility scores of treatment failures by tropism shows that 80 percent of the subjects who failed with X4-tropic virus had susceptibility scores of 0 or 1 compared to only 3 percent that had 3 or more active drugs in their optimized background; 50-60 percent of the subjects who failed with R5 or dual/mixed-tropic virus had susceptibility scores of 0-1 compared to less than 20 percent with susceptibility scores of 3 or more.

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A comprehensive analysis was requested for subjects who had experienced treatment failure and/or changes in their co-receptor tropism. Given the complexity and exploratory nature of the tropism and resistance analyses, sub-studies from clinical studies 1027 and 1028 were proposed.

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A subset of subjects failing with

CCR5-tropic virus were analyzed to identify possible phenotypic and genotypic markers associated with maraviroc resistance in vivo, including determining maraviroc susceptibility in cell culture, the nucleotide sequence of gp120 region to identify amino acids that might contribute to maraviroc resistance, and then nucleotide sequence of the protease and RT genes to identify resistance to drugs in the optimized background therapy mutations.

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A subset of subjects failing with CXCR4-tropic virus were analyzed to ascertain whether the X4-tropic virus emerged from undetected X4-tropic virus at screening or as a result of mutations in a CCR5-tropic virus which causes a tropism switch while on maraviroc. This analysis included evaluation of virus from baseline and on treatment; samples to determine the relative number of X4-tropic and CCR5-tropic viral isolates; nucleotide sequence analysis of the gp120 region to identify amino acid changes that might contribute

to a co-receptor switch; and also phylogenetic analysis to determine the relationship of emerging X4 virus to CCR5-tropic and X4-tropic virus at baseline. In addition, again, the protease and RT were sequenced to determine resistance to the optimized background.

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In the virology subgroup analyses the sponsor selected 267 subjects on blinded therapy from both studies. From this pool, there were 38 analyzed who failed with CCR5-tropic virus. After unblinding, it was round that 13 were on maraviroc and 25 subjects were in the placebo arm.

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The genotype and phenotypic susceptibility to maraviroc of envelope recombinant pseudo viruses was analyzed from these 38 subjects.

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Virus from 2 failure subjects had 3-fold shifts in maraviroc susceptibility at the time of failure. All other subjects on maraviroc had full changes of less than 2-fold, within the normal

range of the Monogram assay.

[Slide]

Viruses from 5 subjects failing maraviroc treatment with CCR5-tropic virus showed evidence of a lower plateau in maximum percentage inhibition rather than full changes in EC_{50} values. The results support previous findings from selection of maraviroc resistance virus in cell culture and isolates from Phase 2 studies that lower plateaus and maximum percentage inhibition were associated with subjects failing maraviroc continued regimen rather than changes in EC_{50} values. All 5 subjects had amino acid changes in the V3 loop of gp120 which were present at failure time points but not present at baseline. Interestingly, these 5 subjects also had lower C_{min} values of less than 75 ng/mL.

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The V3 loop sequences of the viral clones reflected the heterogeneity associated with the V3 region of gp120. All the failure clones had multiple different V3 amino acid changes. However,

changes at either amino acid position 13 or 26 were seen in the V3 loop of gp120 in all 5 of the subjects with maraviroc-associated lower plateaus.

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The role of V3 loop amino acid substitutions in maraviroc resistance was confirmed by site-directed mutagenesis. Mutating amino acids in baseline clones to those seen in resistant clones resulted in a maraviroc resistance phenotype which is less than 95 percent of the maximal percentage inhibition. This shows that these mutations contributed to maraviroc resistance. Back-mutation of amino acid changes of the failure clones resulted in a maraviroc-sensitive phenotype.

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Not all subjects failing maraviroc treatment with CCR5-tropic virus had phenotypic markers of maraviroc. Seven of the subjects receiving maraviroc did not show phenotypic markers of resistance in the Monogram assay. The majority of these subjects, 5 out of 7, had evidence of reduced susceptibility to 1 or more drugs in their

optimized background. This was at either screening or at failure. The CCR5 receptor genotype should be examined from these subjects to see if there is a specific consistent genotype and if maraviroc can bind to these receptors.

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A subset of 20 subjects failing with CXCR4-tropic virus were analyzed and 16 were shown to be in the maraviroc arms and 4 on placebo.

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This evaluation was rather complex so bear with me through this slide. There were 192 pretreatment clones and 48 on-treatment clones from each of the 20 subjects with X4-tropic virus that were analyzed. Shown here is the evaluation of one subject. Each square is a viral clone, with the pink representing R5-tropic virus, the green representing X4-tropic virus, and blue representing dual/mixed-tropic viruses, and the blanks are non-functional clones.

This shows the proportion of R5 and X4 clones at pretreatment and on treatment. Most of

the pretreatment clones are pink, R5-tropic, consistent with this subject being classified as R5-tropic at baseline. Then, all of the on-treatment clones are X4 or dual/mixed, consistent with this subject having failed with X4-tropic virus. So, each of these clones was sequenced. The regions sequenced encompassed the V3 loop of the envelope gene. Phylogenetic trees were generated in using these sequences in order to investigate possible ancestry of the CXCR4-using clones. That is, to determine if the green or X4 clones were related to any of these pink or R5 clones which would suggest a tropism switch, or if the green X4 on-treatment clones were related to any of these green pretreatment clones, which would suggest outgrowth of the X4-tropic virus. The tropism of the clones was confirmed in the validated format of the Trofile Monogram assay.

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In 14 of the subjects CXCR4-tropic clones in the on-treatment sample shared a common ancestor with the pretreatment X4-tropic virus, which

indicates there was outgrowth of the X4-tropic virus. In the remaining 6 subjects X4-using clones did not have a pretreatment X4 ancestor but they were also genetically distinct from the on-treatment and pretreatment R5 population. The V3 loop sequences of these on-treatment X4 clones differed by 7-17 amino acid residues from the V3 loop of the nearest R5 sequence on the phylogenetic tree.

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So, although we cannot rule out a tropism switch whereby the X4-using virus emerged resulting from these 7-17 amino acid substitutions and CCR5 precursor, from the amino acid sequenced differences and phylogenetic tree data, the most likely explanation is that the CXCR4-using clones in these 6 subjects emerged from a preexisting X4-using virus not detected by the tropism assay or the clonal analysis at baseline.

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So, to recap, why did subjects fail on maraviroc? Most subjects, 50-60 percent, failed

with the CSCR4- or dual/mixed-tropic virus in the maraviroc arms. The data from the virology sub-studies suggests that the most prominent reason for failure was outgrowth of X4 not detected at screening. Treatment failure on maraviroc with the CCR5-tropic virus also occurred and resulted from phenotypic and genotypic resistance to maraviroc and/or resistance to the optimized background. It remains to be determined if the host CCR5 genotype also plays a role in maraviroc failure.

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The evolution to a CXCR4-utilizing HIV has been proposed to result in a more virulent virus as it is associated with progression to AIDS. Therefore, there is a concern that using maraviroc will cause outgrowth of CXCR4-tropic virus and will result in worse outcome for patients.

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In studies 1027 and 1028 an examination of the CD4 cell counts by tropism at failure showed that the mean and median change in CD4 cell counts from baseline was lower in those subjects with X4

or dual/mixed-tropic virus at failure compared to those with R5.

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So, we asked for follow-up in the subjects who failed with X4-tropic virus in studies 1027 and 1028. We have requested long-term follow-up on subjects' viral load, the CD4 cell counts, HIV co-receptor tropism and AIDS defining events.

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Twenty-eight subjects failed with X4-tropic virus and were followed by the sponsor. Twenty had at least 1 follow-up visit. Two-thirds of these had changed tropism back to CCR5 or dual/mixed. That leaves 35 percent that still had CXCR4-tropic virus. For the subjects with R5- or dual/mixed-tropic virus at the end of follow-up the median time to last follow-up was approximately 5 months. In contrast, the follow-up for the subjects who remained CXCR4-tropic at the last follow-up visit was 1 month or less. This suggests that over a longer period of follow-up the CCR5 viruses will outgrow CXCR4 viruses in these

subjects. In half the subjects CD4 cell counts also declined, with a mean change of negative 21, and this is consistent with the ongoing viremia in these subjects.

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The viral loads remained similar to the value at treatment failure and did not appear to increase. There were no new category C AIDS-defining events reported for any of the 20 subjects. There were 4 subjects who went on a new antiretroviral treatment and in those 4 subjects the viral loads decreased and CD4 cell counts increased, concomitant with the reduction of viral load.

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So, in summary, 50-60 percent of subjects failed with CXCR4- or dual/mixed-tropic virus in the maraviroc arms. The most prominent reason for failure in these studies was outgrowth of a minor CXCR4-tropic virus population not detected at screening by the Monogram assay.

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Treatment failure on maraviroc with CCR5-tropic virus also occurred and resulted from phenotypic and genotypic resistance to maraviroc and resistance to the optimized background therapy. Again, the role of the CCR5 host receptor genotype is yet to be determined.

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Lower plateaus in maximal percentage inhibition were detected in viruses from 5 subjects failing maraviroc and full changes in EC_{50} values to maraviroc were seen in 2 subjects. Changes in the V3 sequence of gg120 correlated with the presence of lower plateaus and maraviroc resistance. There is heterogeneity of the envelope protein and likely multiple pathways to maraviroc resistance.

I thank you for your time.

Clarifications/Questions

DR. PAXTON: Thank you. Well, it looks like we can now proceed to any clarifications or questions from the committee for the sponsor's presentation or the FDA's presentation right now. Go ahead, Dr. Grant.

DR. GRANT: With regard to efficacy, I would like some more information about reasons for discontinuation in the placebo arm. The data indicates that something like 50 percent of people in the placebo arm discontinued drug somewhere between 8 and 24 weeks and all of them in the primary analysis were considered to have zero virologic response. I am just curious what data there is indicating why they stopped early, and can you provide any assurance that the integrity of the blind was maintained throughout?

DR. PROESTEL: Almost all the discontinuations were related to virologic failure. I think Pfizer may have a slide for this.

DR. MAYER: The primary reason for discontinuations in the placebo group was lack of efficacy as determined by our definitions for treatment failure in the protocol, which was an increase of HIV RNA to 3 times baseline; the inability to achieve a viral load change of less than 0.5 copies/mL by week 8, or a 1-log change in patients who had already had at least a 2-log

change and having had a viral load of less than 400 copies/mL and going to above 5000 copies/mL. So, the primary reason for the discontinuations in the placebo group was lack of efficacy and reaching a treatment failure criterion, and the overall incidence of discontinuations due to adverse events was low and balanced between the 3 treatment groups.

DR. GRANT: Did you collect any information on patient- or physician-perceived randomization group, and were they right in guessing whether they were on the active or placebo arm?

DR. DUNNE: Just to repeat the question, the issue you are asking about is whether the investigators would have been able to guess what the patients were randomized to during the study because of an outcome such as viral load by week 4, or some other kind of phenomena?

DR. GRANT: NoB-well, that is the primary outcome. Actually, my concern would be that there may be subtle issues related to tolerance or symptomatology or some sort of indicator that would

convince the physician or the participant that they were actually on the placebo and that they should get out of the study.

DR. DUNNE: Okay. Dr. Mayer?

DR. MAYER: I would just say that the patients were on 3-6 other antiretroviral agents, including or not including low-dose ritonavir plus blinded drug, either maraviroc or placebo. So, I think that it would have been unlikely for them to have picked out any safety toleration issue and, as Dr. Felstead presented, there really wasn't anything that really indicated a sort of signature safety or toleration issue to the maraviroc.

DR. DUNNE: And just one other thing to add, the reason for stopping therapy on any of the arms was subjectively defined by the protocol with the viral load reduction so there was a natural reason to have the conversation to stop therapy in a patient because of an objective endpoint.

DR. PAXTON: Dr. Dee?

MS. DEE: Yes, I was wondering in the postural hypotension, did you observe that in other

activities, in other words, if people were performing more strenuous activities, or was it just measured or characterized in people that were getting up and down?

DR. DUNNE: Yes, I can understand the question so there are probably two parts to that, how did we assess in our analyses postural hypotension? Was it objectively defined or was there an opportunity for more kind of symptomatic presentation of postural hypotension? I think Dr. Felstead can answer that.

DR. FELSTEAD: Yes, I presented the detailed postural hypotension assessment that was done in the clinic. When patients showed up it was supine, a standing blood pressure was measured and it was defined as any drop of greater than 10 mmHg or 20 mmHg in diastolic or systolic blood pressures where, indeed, a standing blood pressure of less than 90 mmHg systolic was defined as postural hypotension, and that is the primary basis of the presentation. In fact, we agree with the FDA's presentation that we don't see a symptomatic

difference between the placebo and the treatment groups. So, it was very much a specific measurement that I reported today.

MS. DEE: I read your data but I am wondering about people who might be lifting weights or, you know, just doing different sorts of activities than getting up and down. I am wondering about somebody that might have just done some strenuous exercise and what effect that might have as opposed to just sitting and standing.

DR. DUNNE: Sure, I understand the question.

MS. DEE: Suppose you are laying down and lifting weights and then you get up?

DR. DUNNE: Sure, would that have made a difference?

MS. DEE: Right.

DR. DUNNE: Well, it is a good question but I think we were limited in the way we collected information to be able to just report whether patients had a symptom or not. We didn't see anything in the background description of those

events that would tell us it was associated with some kind of physical activity or not, but we understand the question and it is a reasonable one.

DR. PAXTON: Dr. McGowan?

DR. McGOWAN: Just to extend that topic a little bit further, given that the dose-limiting side effect in Phase 1/2 was postural hypotension and you have seen some potentially modest or slight imbalance in ischemic events, what about the recreational use of drugs like Viagra in this population? You must have captured that on conMeds, and did you explore any disparate incidence of hypotension in individuals who did use Viagra? That would be one issue.

Secondly, do you have, or have you plans to explore the physiological responses to co-administration of those two drugs?

DR. DUNNE: Just to repeat the question, can we bring out this postural hypotension effect with other drugs that might affect systemic vascular resistance, Viagra and perhaps other blood pressure medicines, or something like that? Dr.

Felstead, do you want to answer that?

DR. FELSTEAD: Yes, we didn't do a formal drug-drug interaction study within the clinical pharmacology setting but we did review all drugs, including PD5 inhibitors, nitrates, antihypertensives and alpha blockers, and actually looked at those patients as a subgroup. I think I can probably show a slide that would illustrate the data. I think it is S-44, if you could please display the slide?

[Slide]

This is a subgroup of patients. As you can see, we have about 80 patients in the placebo group and 150 were assessed in the QD and BID groups at baseline. These are patients receiving any one of those drugs, and maybe more than one. And, I think at week 2 you can see that there is a slight different between maraviroc QD and OBT between baseline and week 2, and a slight different again in BID at week 2. At week 24 there is maybe a slight difference in maraviroc BID. If we can then show a slide related to that, which is 45?

[Slide]

I think you can see at week 2 and at week 24 the measured postural hypotension in the clinic is actually not greatly dissimilar from the patient population receiving antihypertensives or other potential blood pressure lowering drugs. We also looked at symptomatology in patients with concomitant saquinavir, which I think we just briefly mentioned in the briefing document, to look for outliers as well.

DR. PAXTON: I believe that Dr. Andersen is next.

DR. ANDERSEN: Yes, I had a question about efficacy by race for the FDA. I am looking at table 5. While the numbers of subjects who were Black are small on the study so we are working with that in the two studies, and there is some increase in efficacy with the drug over placebo, within the drug groups the difference is still fairly substantial. I am wondering how a formal analysis was done of an interaction here, and what are the plans for the future for looking at efficacy by

race.

DR. DUNNE: I think Dr. Mayer should be able to respond to that. We have a number of slides that will break down the analysis by race.

DR. MAYER: Can I show slide PE-9, please?

[Slide]

This shows the change in viral load from baseline in Black patients, split out by the total and the number of active drugs included as part of optimized background therapy. If you look to the left on the slide, it shows those patients who had 2 or fewer active agents and the response in Black patients. You recall from the main presentation that this was the subgroup where maraviroc had the greatest efficacy over placebo. So, for Black patients who had 2 or fewer drugs available the change in viral load from baseline was approximately 0.7- to 0.8-log copies/mL benefit for both maraviroc treatment groups compared to placebo.

We think that the overall result in Black patients, which was attenuated compared to the

overall population as shown on the right showing the total response in Black patients, is the result of what is shown in the middle of the slide which only looks at patients who had 3 or more active drugs, which in the overall population showed a modest benefit in favor of maraviroc but here shows that there were 9/23 Black patients in the placebo group that had an unusually high response, almost a 3-log reduction in HIV-1 RNA, compared to the other 2 groups.

So, we think that in the population where maraviroc showed the greatest efficacy in those patients with 2 or fewer active drugs we have an expected response of maraviroc in Black patients that was attenuated because of the unusually high response rate in these 9/23 patients in the placebo group that had 3 or more active drugs.

We also looked at the response in Black patients who had no active drugs available, and the response was as expected. There was a 1- to 1.5-log additional reduction in Black patients who were maraviroc versus placebo. Although small

numbers, we did look at that as well.

DR. PAXTON: Dr. Hendrix and then Dr. Havens.

DR. HENDRIX: This is for either of the presenters on the exposure-response models. You presented the data for the C_{min} and was C_{max} looked at and AUC, and how did those compare?

DR. JADHAV: Yes, we looked at other two important exposure variables, that is C-average and EFFICACY, effective concentration. We find that the response was similar and the relationship was similar. But we selected C_{min} since we were targeting the concentrations and we have to explain in the label that the C_{min} is more amenable in terms of collecting data. But the other exposure variables were consistent with C_{min}.

DR. HENDRIX: So, you also looked at C_{max} and AUC and they were consistent also? I would expect there would be some heterogeneity, enough to not be entirely correlated given the BID and QD data. Was the C_{max} and AUC there the same as the C_{min}? I mean, you looked at those and they were the

same as C_{min}?

DR. JADHAV: We did not look at C_{max} per se but we expected a similar relationship. To note, since we are modeling individualized patients here, every patient contributes within a patient the C_{max}, C_{min} and AUC, they will be correlated within a given patient. If a patient has higher C_{min}, the C_{max} should be higher.

DR. HENDRIX: That would be true for a given dosing frequency but it will vary with different dosing frequencies but that is a minor point.

Let me ask you also, the shapes of the curves were different. It was one of the few things that was very different in the two sets and do you know why that is the case?

DR. JADHAV: Which slides are you talking about?

DR. HENDRIX: Your page 3 and Pfizer's page 31.

DR. JADHAV: Yes, actually I would need a backup slide for that.

[Slide]

In Pfizer's slides what is modeled here is the probability of failure and we wanted to be a little positive so we modeled the probability of success so you have to take it to 1 minus. But noting that, there is a little different in what quantity is being shown here. On Pfizer's slide 62 on page 31, it is consistent with what is the relationship with the observed data. But what I show here is the partial probability. So, when I made a point about different predictors of success, what partial probability does, and this is from our perspective, is it gives you the unique effect of each of the predictors. So, in this, the curve that is shown here or that is shown in Pfizer's slide, it includes the effect of all predictors and there are about 10 predictors of success. What modeling success does is to assess the unique effect of each of the predictors and that is shown here which is, yes, slightly different than the oral. But what is shown in this curve is the unique effect. However, the reserves are derived

from the same data and the same model. It is just a different representation of the same data.

DR. HENDRIX: And the last question is for Pfizer. Was the use of food tracked for the Phase 3 studies so you could include that as an explanatory variable, given that Phase 1 studies showed a 33 percent reduction?

DR. JADHAV: I will comment a little bit and then I will have Pfizer comment more. There was a food effect that was seen on pharmacokinetics. I believe that food was taken into account. When the drug was administered there was no restriction on food. I will have Pfizer comment more on that.

DR. DUNNE: Dr. Mayer can respond to that.

DR. McFADYEN: We did actually track food in the CRF but, because of the QD/BID, the food information that we collected for the QD doesn't pertain to the meal relating to the last dose. So, in our analysis we actually didn't use the food data but we did track it.

DR. PAXTON: It will be Dr. Havens, then me

and then Dr. Rodriguez-Torres.

DR. HAVENS: Table 8 of what we were given shows the data on 150 mg BID and 300 mg BID. I think that was shown in the kinetics analysis. The point here is that 150 mg BID dose gets you to where the percent of patients with less than 75 ng/mL is only 27 percent and the higher dose leaves you with 78 percent under the FDA kinetics target, which shows you that really what we are talking about is that pharmacokinetic boosting by inhibitory drugs gets you into the kinetic target range where you want to be.

So, it would be interesting to see the analyses as boosted versus unboosted because now we are confused. This table 8 did the right thing by separating those 2 groups of boosted versus unboosted and then all BID. When we look at the QD versus BID you can't make sense of that because some of those would have been in the boosted and others in the unboosted, and unboosted is clearly less likely to get you into the target therapeutic range. So, one way to interpret this would be I

would not double the dose. That would not be my approach to trying to think about how to get people into the therapeutic range but, rather, would be to use boosted drug instead of unboosted drug.

That is further shown by figure 1 in the FDA handout data. Unfortunately, this doesn't have page numbers associated with it. I am sorry. This figure, here. I will pass it around. But that shows that C_{max} ranges. It shows it by dose, which is completely misleading because with the 150 mg dose you have to think boosted maraviroc; with the 300 mg dose you think unboosted maraviroc. Then the problem here is that when you use saquinavir/ritonavir, which is really boosted, you get high peaks which is good in terms of control of viremia but perhaps brings you up into this 10 X C_{max} which makes you wonder about the QTc safety.

So, the question would be is it possible to do the analysis instead of QD/BID as boosted versus unboosted, on the one hand, and then QD/BID within those groups? Because when you say 60 percent got to the target trough, that is mixing

groups that are too disparate to mix because they are really using boosted and unboosted which had, based on the data in table 8 that we saw, so dramatically different ability to reach the target trough that you just can't mix them. And, it doesn't matter if you use the 75 ng/ML target trough or 50 ng/mL target trough, which I think could be a reasonable argument, or even 30. But there, in the 300 mg BID which is unboosted drug, only-Bwell, 65 percent were still less than 50. With boosted drug only 17 percent were less than 50.

That would argue perhaps that what you really wanted to do is consider approving the drug only for boosted use. I am really interested to hear the response to that because I am so confused.

[Laughter]

DR. PAXTON: Shall we offer Pfizer an opportunity to unconfuse us?

DR. DUNNE: Yes, we are here to help. So, perhaps we could show you some information on how patients that got a boosted regimen versus those

that did not get a boosted regimen did with regard to the primary efficacy endpoint. I think Dr. Mayer will show us that now.

DR. HAVENS: Then you are going to help me to separate the QD. Because, you see, some of the data would suggest that QD plus Kaletra might give you a high enough trough to be okay. So, I mean, if you boost it the right way once a day might be okay but it is all polluted by the fact that these were mixed together in a way that it makes it impossible for me to really understand it.

DR. DUNNE: Let's have a look at the slide and see if that helps.

DR. HAVENS: Thank you.

DR. MAYER: I showed you a series of slides during my main presentation on the impact of co-administered agents on the efficacy of maraviroc, showing this consistent doubling of response.

[Slide]

If you can just show slide PE-37, this actually shows the percentage of patients that

achieved an HIV-1 RNA of less than 400 copies/mL, broken out by no PI or DELAVIRDINE use and, therefore, a 300 mg unit dose, either QD or BID obviously. Then, in the middle are patients who did receive at least one protease inhibitor other than tipranavir of DELAVIRDINE, and what you can see is that regardless of whether patients received the 300 mg unit dose, on the left, or 150 mg unit dose, in the middle, there was again a consistent doubling of the efficacy in terms of the number of patients who achieved a viral load of less than 400 copies/mL. This was also seen for the other endpoint of less than 50 copies/mL.

DR. HAVENS: So, you are saying that is the boosted in the middle and the unboosted on the left-hand series of bars.

DR. MAYER: Right. The people on the left received basically a non-PI-containing regimen or tipranavir/ ritonavir and not DELAVIRDINE. The people in the middle were people on any protease inhibitor other than tipranavir/ritonavir and/or DELAVIRDINE. On the right is the total population.

DR. HAVENS: Thank you.

DR. PAXTON: Actually, I am going to ask a question myself. We are going to be asked questions about the tropism assay so I want to direct this to I think Dr. Naeger aboutB-sorry, I am just looking for my notes here, we are going to be asked later on to discuss how we would recommend assays for tropism tests to be used for the management of subjects who might receive maraviroc in clinical practice.

So, I had a few basic questions, such as the availability right now of this assay and its approximate cost. You did mention on a couple of occasions that the sensitivity for I think detecting X4 is only about 10 percent. So, I was wondering if you could just give us a little bit more information on some of these basic details that would affect I think what happens in clinical practice.

DR. NAEGER: To my knowledge, I have been told that the assay will be ready. Currently, it is the only one that is ready, although there are

others supposedly in development. Cost? I don't know.

DR. PAXTON: So, the Trofile assay was the only CCR5 assay used in the clinical trials and Dr. Naeger said it should be available for use with the CCR5 antagonist. As far as cost, we don't get involved in that. Dr. Rodriguez-Torres?

DR. RODRIGUEZ-TORRES: Yes, I have a few questions. Some are simple and easy to answer. First, how many Latinos were enrolled in these studies? The answer, I would imagine, will be zero. And why is that, that the population of the United States is not fully represented in the clinical trials of viral diseases? We should have expected Latinos and more African Americans. This is something that I really never understand. I expect that they should be considered to be a priority in the next trials.

I have a question regarding liver diseases, as expected. The results of the data are surprisingly very benign referring to liver abnormalities and I couldn't fail to notice that

only 4-7 percent of hepatitis C co-infected patients were in the maraviroc arms compared to 9 percent in the placebo. Still, the number is very low because in real life we are going to have more than 50 percent of the patients having hepatitis C co-infection.

The first question is do we have any information on the severity of the liver disease in these patients?

Second, why the sponsor, the applicant thinks, or I would like their opinion why this drug is going to behave differently from drugs in the same class that certainly show hepatic toxicity, as vicraviol [ph] and aplaviroc. So, if they have any sense of why this drug will not produce hepatotoxicity. Because my concern is that until we have a real population with more co-infection we really will not know if these patients are going to have more problems.

The third question-Bdo you prefer to answer that now?

DR. DUNNE: Yes, let's try it that way.

So, your first question was about demographics really.

DR. RODRIGUEZ-TORRES: Yes.

DR. DUNNE: How did we end up with the distribution of patients that we did in our clinical trials? We will bring someone up to answer that. Your second question is around hepatitis C background, the degree of liver disease associated with that hepatitis C background and did we observe anything with maraviroc-treated patients in that patient population, given your point there that the exposure was limited to the people that we actually enrolled in the program.

So, to answer maybe the first question I will let Dr. Mayer talk to you about the demographics and what we did to be able to get as many people as possible into the program. Then Dr. Felstead can try to answer the question around liver toxicity and hepatitis C.

DR. RODRIGUEZ-TORRES: No, I understand the toxicity; it was benign. My question is if you had real information on those patients, co-infected

patients, regarding the severity of their disease at baseline, pathology, liver biopsies.

DR. DUNNE: Okay, so a little more information about the patient profiles of the hepatitis C patients as they were at baseline, we will say.

DR. RODRIGUEZ-TORRES: Exactly.

DR. DUNNE: Okay, we will work on that. Dr. Mayer, you are up.

DR. MAYER: So, our intent was to enroll as diverse a population as possible, and to that effort we went to over 200 centers across North America, Europe and Australia to conduct this clinical program. Just to answer your question, there were very few Latinos enrolled in this program and, in terms of the overall demographics, we think that this is roughly comparable to the epidemiology of the HIV-infected population when these patients were diagnosed, which was a median of approximately 14 years ago but, nevertheless, we recognize that we didn't enroll as diverse a population as we had intended and we are fully

committed to obtaining more data on the use of maraviroc in Blacks and Latinos and other populations in future studies.

DR. FELSTEAD: So, just trying to answer some of the questions, I think the first one was about why is maraviroc different from the drug that was discontinued, aplaviroc? Well, it is certainly a different chemical structure and we would expect idiosyncratic drug hypersensitivity reactions in the liver to be driven by structure rather than to be driven by the mechanism of action. And, to our knowledge although, of course, it is limited, I don't think there have been any reports on vicraviol either. Those are the two members of the class that seem to be relatively benign, as far as we know, to the liver and aplaviroc I think was idiosyncratic. But, again, I have limited knowledge on that. But maraviroc is a different structure.

So, I think we regard to hepatitis B and C, you are quite right, we did only have in hepatitis C 4-7 percent of patients who were

hepatitis C co-infected. We are certainly committed to acquiring more information on these groups of patients within any new studies we start, also the expanded access programs, and as part of information through safety registries, etc.

I think related to the severity, we did not get biopsy data at baseline. We did collect HCV RNA data and I think it is in your briefing document. I think in the few patients who were co-infected the HCV RNA is probably largely unchanged, maybe a small reduction in the maraviroc treatment arms.

DR. RODRIGUEZ-TORRES: You don't have data on pathology?

DR. FELSTEAD: We don't, not pathology on entry into the study.

DR. RODRIGUEZ-TORRES: The last question I have for the applicant is regarding the outcomes of the patients that switched to the X4. I imagine that this is going to be a topic of a lot of discussion this afternoon, but is there any way we can have longer duration information? Because you

have been following those patients, is there any opportunity to see what has happened with those patients, besides the information that the FDA has?

DR. DUNNE: I think at this point we have provided all the information that we have, given that we are trying to bring the drug to patients with the medical need as soon as we possibly can. We agree with you though that we can't answer the question now about impacts in the long term--

DR. RODRIGUEZ-TORRES: Exactly.

DR. DUNNE: B-about transient switch to X4. It is a good question and in our risk management plan that we have laid out we are committed to following people for significant periods of time to see if something different happens in people who have a switch versus people that don't.

DR. RODRIGUEZ-TORRES: Because I am not an expert but I imagine that malignancy and other immune diseases could occur later. So, we don't have a sense of that.

DR. DUNNE: Yes, we need to continue to

follow patients for longer periods of time, and we plan on trying to do that as part of our risk management plan.

DR. PAXTON: Our list of people wanting to ask questions is growing. We haven't forgotten about you. Dr. Yarchoan then Dr. Gibert and Dr. Weiss Smith.

DR. YARCHOAN: I have two questions. The first is really, I guess, both for the agency and the company. The whole impetus for this class of drugs came from the observation of delta-32 CCR5 in resistance to HIV progression and the fact that these people apparently led normal lives. Since that time, there has been some emerging data about people with this genetic tree in specific diseases looked at. In some cases it has been protective, interestingly enough in AIDS lymphoma. In other cases though it seems to incur increased susceptibility. One example of this is West Nile disease where some studies, by Phil Murphy and colleagues, have shown an increased incidence of symptomatic disease and perhaps an increased

incidence of death from this, and for breast cancer there is also some evidence.

So, I am wondering if there are any comments that you would want to make about some of the specific, perhaps rare infections or diseases such as West Nile virus and how that might be monitored.

The second one just relates to the cholesterol. It was interesting that the fold increase seemed to be more affected by the drug than the absolute values. Was there an imbalance at entry, and cholesterol effects that might occur over a long period of time and how would this be monitored?

DR. DUNNE: In review of the adverse event database for the two pivotal trials there were no episodes of West Nile virus. An assessment was done of CNS infections of any sort to see whether or not there was simply a decrease in surveillance that might allow for, I guess, an imbalance in CNS infectious events. There were only 4 events in the 2 pivotal trials during double-blind phase, 2 viral

meningitis, 1 suspected neurosyphilis, and 1 event of PML. These were all in the maraviroc arm. But when you take into account the fact that there was a 4:1 randomization, you know, essentially if there was a single event in the placebo arm maraviroc becomes--

DR. YARCHOAN: So, I mean, in a small trial like this you actually wouldn't expect to find any. The question is as you have relatively rare diseases and the drug is used in the country how might one look for this? It wouldn't be a classic drug toxicity; it would be an increased incidence of a background disease.

DR. DUNNE: Yes. We agree, yes. We can only report on what we have seen here, and it is the exposure that it is. These are uncommon events overall. So, we accept that completely. Again, I come back to the risk management plan that we have committed to now to be able to follow people longer in greater numbers, and there are different databases that can be tracked to be able to pick up rare events. It is not a perfect way to do adverse

event monitoring in the long term but at least you might get a rough sense of things.

Perhaps one thing we could do, because I think the committee will probably be interested in this at some point, is just put up a slide or two on what is the West Nile virus connection; what is the breast cancer connection, just so people get refreshed on what that might look like. Would you like to do that?

DR. FELSTEAD: I think in terms of the West Nile, at the moment it is a single unreplicated study so there are some limitations in terms of it is a cohort analysis. And, as you say, we are committed to following it in the risk management program. It is a pretty rare infection and the intersections between patients who have HIV and West Nile virus is going to be quite challenging to study epidemiologically, including if you then subset out the ones that are receiving maraviroc versus the ones that are not receiving maraviroc. One hopes that if a patient is receiving maraviroc, that in the future they would have a very low viral