atazanavirB-plausible alternative explanations. Two had elevated levels in the setting of shock and two had elevated levels in the setting of viral hepatitis B activation.

[Slide 45]

Dr. Hy Zimmerman, who is a noted hepatologist, observed that serum transaminase elevations, accompanied by elevated bilirubin in the absence of biliary obstruction, is a powerful predictor of serious hepatotoxicity.

[Slide 46]

As previously noted, the definition for potential Hy=s Law cases consists of AST or ALT levels greater than or equal to three times the upper limit of normal; total bilirubin levels of greater than or equal to two times the upper limit of normal; no evidence of obstruction and no evidence of an alternate plausible explanation. We examined the Phase 2 and 3 data sets using the safety update report data, and there were six subjects who met the initial laboratory screening criteria.

[Slide 47]

This slide provides several details on these six subjects. However, each case was confounded by either use of atazanavir or a confounding illness and we are in agreement with the applicant assessment that no cases satisfy the definition for Hy=s Law.

[Slide 48]

Analysis of creatine kinase elevations was performed using the safety update report database for the Phase 2 and 3 studies, and 6.6 percent of subjects in the raltegravir group had grade 2 to 4 CK elevations versus 4 percent in control.

[Slide 49]

The majority of elevations were transient and resolved without drug interruption. There were no serious adverse events or study discontinuations associated with elevated CK levels, and there was no apparent association with concomitant use of lipid-lowering agents, PIs and increased CK levels.

[Slide 50]

Potential associations with renal events

were explored in the Phase 2 and 3 studies. No overall imbalance was identified between the two groups, and there was no apparent pattern to the types of renal adverse events observed.

[Slide 51]

Six renal serious adverse events occurred, all in the double-blind period. All had plausible alternative explanations, either due to concomitant medications such as tenofovir, and/or underlying medical conditions such as kidney stone, viral hepatitis, hypertension and diabetes.

[Slide 52]

As previously discussed, atazanavir increases raltegravir levels and, therefore, an analysis of adverse events occurring in this subset was performed. With the exception of known atazanavir-related effects, no other adverse events were present in greater frequency in subjects on atazanavir compared with all raltegravir-treated subjects.

[Slide 53]

Subjects with hepatitis co-infection had

elevated transaminases and bilirubin compared to all subjects in the Phase 3 studies. However, there were no study discontinuations due to elevated AST, ALT or bilirubin.

[Slide 54]

The final analysis I will present consists of adverse events associated with high raltegravir plasma concentrations. Subjects with the highest plasma concentrations were examined for any potential notable adverse event. As mentioned previously by the applicant, high within subject variability has been observed and, because of this variability, only the adverse events occurring within two days of the higher raltegravir levels were examined. Using this definition, three adverse events were identified occurring in more than two subjects, cough, lymphadenopathy and rash. None were serious and none resulted in study discontinuation. Therefore, using this analysis no temporal correlation between adverse events and higher plasma concentration was established.

[Slide 55]

[Conclusion]

[Slide 56]

In conclusion, raltegravir has robust antiviral activity with no clearly identified safety signals. Relatively few subjects discontinued due to adverse events. In regards to malignancy, initial observed imbalance has diminished with longer follow up. We acknowledge the safety data was limited by small population and short follow up, however, we performed a thorough analysis of potential important safety events and in our assessment no clear safety signal has emerged given the currently available safety data.

That said, and especially because this is the first integrase inhibitor, ongoing safety assessments will be performed as more information on raltegravir use is received in the future, and I really appreciate the opportunity to speak. Thank you.

DR. PAXTON: Thanks very much, Dr. Connelly. It is now ten o=clock so what we will do is we will take our break now and then come back in

half an hour and go into the clarifications and questions section of the day.

[Brief recess]

DR. PAXTON: As everyone is finding their seats, I am going to allow one final member of the Antiviral Advisory Committee to introduce himself. Dr. Hendrix

DR. HENDRIX: Craig Hendrix, from clinical pharmacology at Johns Hopkins.

Clarifications/Questions

DR. PAXTON: Thank you to both the FDA and to the applicant for such clear presentations this morning. We are now going to move into clarifications and questions from the panel to the sponsor and to the FDA. I would like to ask could you make it clear when you pose your question who you are directing it to, the FDA or the sponsor. I am going to open this up now for the questions. Dr. Grant?

DR. GRANT: First of all, I thank the presenters for excellent presentations. It really does help to get through a lot of material.

The malignancy question I think needs to be discussed, and I appreciate the follow-on data which really does help establish that the rates of malignancies are comparable in the two groups. When I look at the types of malignancies in the two groups, control versus raltegravir, it seems like Kaposi=s sarcoma is over-represented in the raltegravir group. So, my question really is to the sponsor. Have there been any studies or sub-studies looking with more active skin surveillance for evidence of subclinical Kaposi=s sarcoma in the context of any of these clinical trials? And, are there any plans in the post-marketing surveillance for looking specifically at Kaposi=s sarcoma using active skin surveillance in those who are seropositive?

DR. ISAACS: In the development program we did not specifically look for cancers in the way that you are suggesting. The cases were spontaneously reported by the treating physicians. But just to put the rate of Kaposi=s into some perspective, could I preview slide 1516?

[Slide]

Thank you. This was shown in the background document. This is a summary table of the incidence rates of malignancies in the raltegravir group compared to the rate ranges from the published literature. You can see that we went to numerous sources to generate these ranges from the published literature.

I just wanted to make two points. The more general point is that the rate in the raltegravir group of 2.3 per 100 patient-years is right in the middle of the published rate range. The second point that I wanted to make specifically with regards to Kaposi=s sarcoma, which was your question, is that the rate that was seen in the raltegravir group is actually towards the lower end of the range reported in the literature and does not represent a specific signal with regards to Kaposi=s sarcoma.

While I have the slide up I just wanted to take the opportunity to make two other more general points that don=t specifically relate to your

question. The first is that when we noticed this imbalance and did the comprehensive review we wanted to be as inclusive as possible. Actually, we included cases of carcinoma in situ for the anogenital squamous cell carcinomas to be as inclusive as possible. There were actually three in the original filing and four if you count all the accumulated data that we have shown. So, the squamous cell carcinoma anogenital rate there is inflated by having, in fact, included pre-malignant conditions.

The second point I wanted to make is that non-melanoma skin cancers are notoriously under-reported in published studies so that the rate there, although slightly on the high end of the published rate, probably does not represent a specific signal.

DR. PAXTON: I believe that Dr. Havens had a question.

DR. HAVENS: Thank you. It is a question for the sponsor. Are you asking to have dose modification for your drug when given with

phenobarbital, Dilantin or rifampin?

DR. ISAACS: As we showed the data earlier, there is a modest reduction in raltegravir levels when co-administered with rifampin, presumably on the basis of rifampin=s general inductive effects on drug metabolizing enzymes. At the time that we submitted the application, including the background document, we had proposed, in the absence of any clinical data, to support no dose adjustment; that it might be wisest to consider doubling the dose of raltegravir. Since the background document was submitted we have had continuing discussions, both internally within the company and externally with consultants, and we are in the process of reassessing that recommendation at this time, which is why it was not made in my presentation. We have an ongoing study, Phase 1 study looking at doubling the dose of raltegravir in the presence of rifampin, and those pharmacokinetic data are in the process of being analyzed and will be shared with the agency as soon as we have them. So, at this point we are not making a specific recommendation

with regards to rifampin and are waiting to discuss that with the agency.

DR. HAVENS: Do I get a follow-up question? I note on page 30 of the background information in the comparison of the C_{12}, which is the kinetics target that you suggest is most important and drove early development, that tipranavir, ritonavir and rifampin share similar effects, measured both by the point estimate and the 90 percent confidence interval, on reducing raltegravir C_{min}. Without using words like Aslight@ but just sticking with data, do you think there is a significant difference between tipranavir and ritonavir on their effects as shown in that table?

DR. ISAACS: So, I believe the table you are referring to was the table that I showed in my presentation.

DR. HAVENS: Well, the table that you showed in your presentation didn=t have the confidence limits.

DR. ISAACS: I am sorry.

DR. HAVENS: It is okay.

DR. ISAACS: So, two points. The first is that in terms of comparison you are correct that the effects of tipranavir, ritonavir and rifampin on the $C_{12\text{-hours}}$ are similar. The difference is that with tipranavir we had clinical data from the Phase 3 studies which showed that tipranavir, in combination with raltegravir 400 mg BIDB-could we preview slide 416, please?

[Slide]

These are the data that were in the backgrounder. I just mentioned it but I didn=t show it previously. You can see that when tipranavir is not in the optimized background regimen the rate in the raltegravir group, in yellow, is 81 percent less than 400 at 16 weeks. But when you include tipranavir in the optimized background therapy with raltegravir the rate does not change.

The other piece of information on the slide relates to those patients who actually had HIV that was resistant to tipranavir by genotype, and this is a particularly stringent test because

in most patients, first, they would not have had the protease inhibitors because the protease inhibitors cannot be used in general with tipranavir and, secondly, tipranavir is not adding anything, or at most a little bit to the efficacy, but at the same is reducing the raltegravir levels. So, it is not surprising that the overall response rate is lower because there is less active drug in the regimen but the treatment effect between the raltegravir and the placebo group is maintained in that. So, based on the totality of that data, we felt that the clinical data support not having dose adjustment with tipranavir.

The difference with rifampin is that we specifically excluded rifampin, phenobarbital and phenytoin from the clinical program so we have no clinical data which tells us whether the effect of rifampin on raltegravir levels would or would not be clinically significant. That is why we took the original conservative position to recommend the dose increase which, as I said a minute ago, we are now reconsidering.

DR. HAVENS: Now, the comparison you make here between 80 and 44, or 86 and 48B-let me ask you to make the comparison between the 81 and 56. That is to say, if you didn=t get tipranavir and the OBT versus tipranavir-resistant what you are saying is there is, as you point out, less effect of tipranavir and less effect of raltegravir because of the effect of tipranavir on decreasing raltegravir exposure. So, you would have to look at this by active agents in the OBT. Since some of these people are on up to seven agents you can=t know unless you show us the data there. So, to say that there is good clinical data I think is impossible for me to exactly see because if I compare the people who got tipranavir plus raltegravir who had 56 percent good outcome to the people who got neither one of those, that 56 percent, for me, suggestsB-5 to 81 comparison--suggests a potential different decrease in effectiveness when raltegravir is used with concomitantly administered tipranavir.

DR. ISAACS: I understand the point that

you are making. I cannot quote to you the exact number of active drugs in the regimen but I can make the general point that the patients receiving tipranavir in the setting of virus which is resistant to tipranavir have less active agents than those that are in the other group.

DR. HAVENS: You need to show the data for that because, since they were on potentially up to seven in the OBT and raltegravir added nothing, if there were at least three in the OBT it is possible that they had more than that and the tipranavir was actually subtracting from the effectiveness of this very effective drug.

It is a great drug. It is wonderful to see this level of detail, but it is very concerning in terms of whether or not you should use it with tipranavir or rifampin, and unless we know the OBT for that crowd we aren=t able to interpret those data.

DR. PAXTON: The next person was Dr. Gordin.

DR. GORDIN: Actually, I wanted to push the

same issue with rifamycins. Do you have plans to investigate rifobutin or rifapentin? Rifapentin right now is not indicated for HIV-infected people but there is a large 8,000-person CDC study looking at it for treatment of latent TB which does include HIV-infected individuals so it would be very important to understand the interactions of all the rifamycins so what plans do you have to investigate that?

DR. ISAACS: I cannot comment specifically on rifapentin. We have not discussed that previously. But with regards to rifobutin, the magnitude of the effect is expected to be less and we have allowed the use of rifobutin with raltegravir in the clinical development program. I don=t have enough data that I can share with you with regards to that. We do not have a specific Phase 1 study on that. We will attempt over the next hour, so that after lunch, to see if we can find the data that was requested previously with regards to those patients.

DR. PAXTON: Next up is Miss Swan.

MS. SWAN: Thank you. I have a question for the sponsor about resistance. There was am abstract presented at the resistance meeting on mutations related to HIV integrase inhibitors being associated with reverse transcriptase mutations in HART-treated patients. On page 74 of your background material there were five treatment-naive patients that failed. Two had no mutations in the integrase region but did have reverse transcriptase mutations and phenotypic resistance to 3TC. Two had mutations in both reverse transcriptase and integrase. Can you explain this?

DR. MILLER: My name is Mike Miller. I am from the antiviral research department and I would like to try and answer your question. Could we preview 1618, please?

[Slide]

This is a summary slide. It doesn=t have the phenotype data but it has the genotypic data that you are requesting for the treatment-naive study protocol 4. It is broken down on the left by patients according to dose. So, there was one

patient who received 100 mg who had virologic failure; four patients who received 200 mg who had virologic failure; and there was one virologic failure in the efaverenz arm. What we list out here are the mutations that were observed in the integrase gene for all those patients, also mutations that are known to affect 3TC, tenofovir and efaverenz. You correctly summarized the data.

So, in all but one of these patients we saw evidence of emerging 3TC resistance. In only two of the patients we saw evidence of emerging tenofovir resistance. In two of the patients we also saw evidence of raltegravir resistance. There was one patient who had no mutations in the integrase gene but, likewise, did not have any mutations in the RT gene that was consistent with resistance with either of those agents. So, this is a patient who failed therapy without developing resistance apparently to any of those active agents. In the case of the other patients, you can see that the one on the top developed resistance to all of the agents that he was receiving. For the

first one in the 200 mg arm there was only evidence of emerging 3TC resistance and not tenofovir or raltegravir resistance.

So, the only thing that I would like to point out about this is that this is fairly early in the study and it is possible that with additional genotyping and longitudinal data we can learn more and we might eventually actually see the emergence of resistance in some of those patients.

MS. SWAN: Just to follow up, are you planning to study this more thoroughly?

DR. MILLER: Yes, we are collecting longitudinal genotype data in all of our ongoing clinical studies so we should be able to shed more light on that.

DR. PAXTON: The next person is Dr. Yarchoan.

DR. YARCHOAN: Yes, I have a question, actually one for the agency and one for the sponsor, about the malignancies. Part of it is that it has been a little bit hard to look at the different numbers presented in different analyses

of the data and really try to get a sense of the broader numbers there. In part, it is because often the number of malignancies were presented without the background numbers and I was just wondering if you could sort of walk me through that a bit.

In your background you initially mentioned that there were 20 malignancies in 19 subjects on the drug but none in the placebo groups and it really wasn=t clear what the denominator of patients treated was and whether that was statistically significant.

Then, there was talk about a follow up where there were, again, 19 patientsB-one less patient with 21 malignancies. So, it wasn=t clear how this group was different and how it was that in a longer analysis there seemed to be less patients with malignancies. Maybe there was a group that was included in this analysis. I was just wondering if you could walk me through it.

Then in a related thing for the company, you talked about the statistics on the

patient-years but I was wondering if you also did on the number of patients and the idea that there could be a one-hit phenomenon.

Also, there were some animals that developed malignancies, squamous cell carcinomas, and what your thinking is about that and the relevance or lack of relevance to the clinical data.

DR. CONNELLY: I will try to address each of your points. I recognize that some of the definitions can overlap.

DR. YARCHOAN: Twenty to zero sort of jumped out.

DR. CONNELLY: Right. So, the initial information that we reviewed in detail came from the safety update report and that was the February, 2007 cut-off and we received that information I believe around June. At that point the applicant presented to us all the available malignancy data and what I described included the malignancies without regard to the time of occurrence during the protocol, so without regard to double-blind, and it

included all the open-label. So, that accounted for a higher number in the overall descriptive portion of the backgrounder.

Then, when I did the malignancy rates to try to have a more balanced comparison I limited it to the double-blind phase. That is what the analysis is in the backgrounder, based on the February, 2007 data where there were a total of 13 malignancies in the raltegravir arm versus zero in the placebo, limited to the double-blind phase.

Then, using the July update, and now I will refer to slide 32 that I presented today, I incorporated some more recent information and the 36 and 31 subjects accounted for both the double-blind and the open-label phases and I have listed them on that slide and also the descriptive slide 33. However, then I did the analyses trying to account for exposure, again limited to those occurring just in the double-blind phase.

DR. YARCHOAN: Right. So, in the first one if you just did patients rather than patient-years is there a statistical significance there or not?

DR. CONNELLY: I did not do any statistical analysis so in the first one-Bthe first one meaning based on the July data--

DR. YARCHOAN: The 13 versus zero.

DR. CONNELLY: Yes. I apologize, I don=t have that in front of me now but the placebo would have been still zero percent and it would just be 13 divided byB-I am sorry, based on patients the denominator 595 in the backgrounder is the number of patients. So, that is not adjusted for exposure. So, the 2.2 percent is just based on total treatment-experienced patients in protocols 5, 18 and 19.

DR. YARCHOAN: But is that difference based on number of patients significant, statistically significant?

DR. CONNELLY: Because there were such small numbers I did not perform a test of statistical significance. I felt that just the numbers were enough to highlight a concern that warranted further information regardless of what the statistical results would have shown me.

DR. YARCHOAN: Thank you.

DR. ISAACS: I believe the other question you asked related to the interim results from the carcinogenicity studies in animals.

DR. YARCHOAN: Yes, just to give that some context for us.

DR. ISAACS: So, as was presented in the background document, the carcinogenicity studies in rats and mice are ongoing. In the rat study, in the female high-dose animals, there were cases of squamous cell carcinoma identified in the nasopharynx of the animals. These are not felt to be evidence of a systemic cancer risk but, rather, related to direct deposition of raltegravir into the nasopharynx as part of the administration of the drug to the animals. Raltegravir has been demonstrated to be a direct irritant and these animals are receiving the highest dose and the highest concentration per milliliter. So, it is thought to be a direct irritant effect, inflammation leading ultimately through metaplasia to neoplasia and not evidence of a systemic cancer

signal.

DR. YARCHOAN: Is there any evidence of that in the GI tract? Presumably, patients are going to be taking this orally.

DR. ISAACS: Yes. So, we looked very closely at evidence of GI toxicity in the clinical studies for reasons including the one you just asked, and the drug was very well tolerated in the GI tract. There were very few symptoms related to upper GI or lower GI toxicity, except for diarrhea which was common in both the raltegravir and the placebo group.

DR. YARCHOAN: Thank you.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: Yes, this is directed to applicant. I am actually looking at three different pages of the presentations here. Probably the best one to use is the FDA=s summary slide 12, page 6 of the materials presented today.

My question relates to the intended use in a broad range of subjects called treatment-experienced here. However, the results

in subjects who had three or more agents active in their optimized regimen show no real difference between the two arms, albeit in a small number of subjects. Additionally, in the background information on the 004 protocol that was in naive subjects there was no difference between the two arms.

So, the question I would ask is whether a broad indication in all treatment-experienced subjects is, you know, really reasonable here. If somebody has already got a very active regimen available to them, do they need this added to it?

DR. ISAACS: So, the question that you are asking really relates, based on the data that we currently have, to what is the best place for raltegravir to be used. Can I please preview slide 43?

[Slide]

Thank you. This is the slide that we showed earlier this morning with the HIV less than 400 copies at week 16, and it is essentially complementary to the table that you referred to,

except the agency=s data was less than 50 copies/mL I believe.

DR. ANDERSEN: And the agency also broke out two versus three or more.

DR. ISAACS: Before I forget, we actually combined two and three because the number of patients with three was not very great and the results in the patients getting two or more drugs were similar.

I think that there are two key points on this slide and I think they are consistent with the comment you just made. The first is that in patients who had limited or no activity in their optimized background therapy, in this case demonstrated by GSS score of zero, the placebo group is responding very poorly, with a response rate of only 110 percent of the patients having less than 400 copies at week 16, whereas the raltegravir group is having a response rate of 57 percent. However, this is essentially a setting of functional monotherapy and in treating patients with HIV disease one is trying to get a prolonged

response, and in order to do that you need to have combination therapy and not monotherapy. So, the data in the GSS scores of 1, 2 or more, which are very similar for the raltegravir group, indicate that when raltegravir is combined with at least one other potent active agent you can achieve response rates in these heavily treatment-experienced HIV-infected patients of over 80 percent, and not dissimilar to what you can achieve in treatment-naive patients with the currently available regimens.

Overall, the data support that raltegravir in this setting is most appropriately used in combination with other drugs, and that the indication in treatment-experienced patients seems to be the most appropriate indication based on the data that we have.

DR. PAXTON: Dr. McGowan?

DR. McGOWAN: I just had a couple of follow-on safety questions. The first really was just an issue of pharmacogenomics I suppose really, and I wanted to ask the sponsor about the research

so far in evaluating the safety database in terms of UGT1A1 *28 homozygocity and perhaps a predilection to have enhanced safety issues, as has been reported in other drugs like irinotecan. That is my first question, if someone wants to respond to that. There was mention of a genotype study in the briefing document.

DR. IWAMOTO: My name is Marian Iwamoto, from clinical pharmacology. With regard to UGT1A1, indeed, we did do a separate study. Just to clarify for the committee, there is a significant portion of the population that is affected by polymorphisms that decrease UGT1A1. That is why we conducted that clinical study.

We studied individuals that were homozygous for the *28 population since it represents the polymorphism that is relatively common but results in significant reduction of UGT1A1 activity, for example, compared to heterozygotes. We have the updated pharmacokinetic data from that study. May I have slide number 961, please?

[Slide]

What we see on this slide along the X axis is two groups of individuals being compared. On the left side, the individuals are homozygote for *28 polymorphism and on the right are the individuals with wild type UGT1A1. Along the You axis is the $C_{12\text{-hour}}$ concentration or trough concentration. What we see here is that overall the comparison of $C_{12\text{-hour}}$ is relatively comparable in the two groups of individuals. I would also like to show the data for the exposure as well which is more reflective of safety. May I have slide number 960, please?

[Slide]

Again, what we see is the comparison of the two groups along the X axis and then along the You axis is exposure. Once again, the exposure comparison between the two groups of individuals is relatively comparable, signifying that the individuals with the UGT1A1 *28 polymorphism do not have increased exposure to raltegravir.

DR. HAVENS: Could I have you go back to

the slide before and give us the mean numbers, which were hard to tell based on just looking at the slide?

DR. IWAMOTO: I am sorry, the $C_{12\text{-hour}}$ data?

DR. HAVENS: Yes. The reason I ask for that is because in the backgrounder you say that is the kinetics target of most importance to outcome, and it looked like there was about twofold or greaterB-I just couldn=t know from looking at the slide. If you could just tell us the numbers, that would be helpful.

DR. IWAMOTO: Slide 961, please. I apologize.

[Slide]

DR. HAVENS: What is the geometric mean in *28?

DR. McGOWAN: It looks like 110 versus 50.

DR. HAVENS: So, about twice. Thank you very much.

DR. McGOWAN: But I am not a representative of the company.

DR. HAVENS: I understand. That is

probably why you didn=t say Aslight.@

DR. IWAMOTO: The geometric mean for the UGR1A1 *28 group was 113 and in the wild type it was 59.4.

DR. HAVENS: Very good, Dr. McGowan!

DR. ISAACS: I believe there was also a question about the safety. Was your question directed to the safety in the clinical population as well?

DR. McGOWAN: It was really based on the irinotecan literature about an increased risk of hematological toxicity and just as an expression of the genotypic variability in your population, and I don=t know to what extent you are combining genomics with safety assessment in the Phase 3 database, or if you have collected samples needed to do that, and were you proposing to do any of those types of studies.

DR. ISAACS: We have colleted the samples. We have not done any pharmacogenetic analyses. The overall safety profile did not point us in the direction of doing those analyses.

DR. McGOWAN: An unrelated question was really just about some data in one of the FDA tables which I thought was a little unusual. The apparent high incidence of herpes zoster in the raltegravir group compared to placebo is really quite striking. I think there were 21 cases. It was 4 percent in the active arm and 2 cases, 0.7 percent in the placebo arm. So, even when you adjust for period of exposure time on drug, there seems to be quite a difference.

DR. ISAACS: I will answer that question about the herpes zoster. Can we, please, show slide 661?

[Slide]

This is a summary of the herpes zoster cases and this is based on our original NDA analysis but, as was mentioned previously, the SUR data, the safety update report data, is very similar to the original analysis that we performed on the original data sets provided. There is a greater incidence of herpes zoster in the raltegravir group versus the placebo group.

Just as a general comment, when you are looking at a large number of AEs it is not unusual to see from time to time one AE that seems more common than the other. We did look at the crude exposure adjusted rates, and for the raltegravir group it is 6.5 cases/100 patient-years and for the placebo group it is 1.6 cases/100 patient-years. To put that into some perspective, there is actually quite an extensive literature on herpes zoster in HIV-infected patients and, interestingly, the case rate in patients who are not treated with highly active antiretroviral therapy tends to be lower than the case rate reported in patients who are treated with highly active antiretroviral therapy. The 6.5 cases/100 patient-years in the raltegravir group is actually at the low end of the rate that is reported for people on highly active antiretroviral therapy, which ranges from approximately 6-22 cases/100 patient-years depending on the literature source.

So, overall, these cases are consistent with what one would expect in this population

receiving a highly active regimen, and the difference between the raltegravir and placebo group may actually reflect different response rates in the groups, leading to a higher rate in the raltegravir group because of the antiretroviral response they are getting.

DR. PAXTON: Dr. Glesby?

DR. GLESBY: I would just like to get back to the issue of malignancies. My question is directed to the sponsor. If the FDA has anything to add, I would appreciate their comments. Was any statistical test done to look for an interaction between the time of diagnosis of the malignancies in the treatment arm? And the follow up would be is there anything in the clinical presentations to suggest that there may be manifestations of immune reconstitution in the raltegravir recipients?

DR. ISAACS: So, your question is alluding to the fact that many of the cases in the raltegravir group were diagnosed within the first three to four months of starting therapy as opposed to those in the placebo group. If we could show

slide 69?

[Slide]

This is a slide which Dr. Nguyen showed this morning, just to provide the perspective. The third column under each of the raltegravir and the comparator groups refers to those cases that were diagnosed within the first three months on therapy. This data is based on the cumulative update as of July 9th and double-blind comparative data. Over half of the cases in the raltegravir group were diagnosed within three months of entry into the study. Several of those though included recurrent cancers. Overall, we feel that this represents a small number of cases and that there is not an association with early cases and raltegravir use; that overall raltegravir is not associated with cancer causation.

We did look very closely at the issue of immune reconstitution syndrome in the patients and looked both at investigator-reported immune reconstitution and also specifically looked at viral response rates and changes from baseline in

CD4 cell count in these patients. One of the patients, the patient with the paracellular carcinoma was diagnosed in the context of an investigator-reported immune reconstitution syndrome. Most of the patients also had a virologic response but less than half of the patients actually had a rapid CD4 cell count response. So, it is possible that immune reconstitution is associated with a small part of these cancers but it is not associated with all of the cancers.

DR. PAXTON: Dr. Havens, did you have another question? If not, I will skip over you.

DR. HAVENS: I have a lot of other ones but I wanted to make sure that everybody got a chance to talk a little bit.

DR. PAXTON: Then we will come back to you and we will go to Dr. Gordin.

DR. GORDIN: This one I guess is for the agency. Do you have guidelines for what you consider is a reasonable or adequate number of patients in follow up for certain durations that

you either discuss with companies or make public? I am somewhat concerned that, according to the sponsor on one of their slides--53--only 134 patients have been followed for 48 weeks. So read literally, the guidelines that they would use for using this drug would be extremely broad. For anybody who has ever taken any medicine and is currently failing, even inadequate therapy, it would be an indication for use of the drug, yet only 134 patients have been treated for 48 weeks. So, what is your sense of the adequacy of that follow up?

DR. MURRAY: Well, in the guidance from the International Committee on Harmonization for non-life-threatening diseases the standard would be about 300-600 at six months and at least 100 patients followed for a year with 1,500 patients with any exposure at all, and that would be for a non-serious life-threatening disease. So, we have more flexibility in this. You are right, it is really not a lot of data to make, you know, some safety assessments or look for long-term signals

but it does fit in with the guidelines, international guidelines.

DR. CONNELLY: I would just like to add one follow up, that using the safety update report database and accounting for longer exposure, those that received the 400 mg dose for at least six months were 507 in the treatment-experienced, and if you include the naive at the 400 mg dose it increases to 548. And, that was reviewed so we do have do fulfill at least six months of safety data.

DR. PAXTON: Dr. Andersen?

DR. ANDERSEN: Yes, I would like to return to the question of the broad indication for all subjects who have received prior antiretrovirals. Protocols 018 and 019 were focused on subjects who were resistant to at least one drug from each of the three classes so representing potentially, you know, a heavily pre-treated population. Again, I am cross-referencing here and doing some numbers, looking at applicant=s backgrounder on page 64 and the 400 copy cut-off and the 50 copy cut-off. Again, I am looking at those with a PSS of 3 or

more and it looks like there is not a substantial difference between the two arms there and that is in-Bwhat?-B133 subjects, which is how many people we have the 48-week safety data on.

So, again, my question is, is this appropriate to be used in, say, somebody who is having second-line therapy, somebody just failing their first regimen where they have only seen two classes of drug?

DR. ISAACS: The indication that we have asked for is, as you note, in treatment-experienced patients. I think in making decisions on these data one needs to think about how best to construct a regimen for the patient and the need to have multiple active agents in that treatment regimen. I do understand the point that you are making, which is that with the indication that is proposed it is possible that it may move away from these heavily treatment-experienced patients, which represented about a third of the patients who were studied in the Phase 3 program, but there were two-thirds of the patients for whom we were able to

construct an optimized background regimen that contained at least one other active component.

In addition, there are other reasons for patients to stop therapy, including intolerance of antiretroviral agents. So, the overall data, to our mind, does support the indication that we have asked for. As was indicated in our background package and very briefly in the FDA background package, we also have data from a Phase 2 treatment-experienced study which is ongoing which provides information in less treatment-experienced patients, and an ongoing Phase 3 study in treatment-naive patients to gain greater experience. The overarching concern from our perspective is to be able to construct the best possible regimen for patients, and we do believe that the data support the indication that has been proposed.

DR. PAXTON: Dr. Grant?

DR. GRANT: On the same theme of activity in those with PSS greater than 3 or GSS greater than 3 in treatment-experienced patients failing

therapy who still have a GSS greater than 3 the question of adherence really comes to mind. I think that it is going to be very difficult to demonstrate differences in treatment regimens if adherence is moderate or poor.

So, the question to the sponsor really is do you have data regarding adherence in your trials, and can you break that adherence data down by GSS and PSS? If you have that data, could you present it?

DR. ISAACS: We did collect compliance data in the clinical studies. If we could look at slide 819, please?

[Slide]

This is data from the Phase 3 studies based on our original filing. It shows patient compliance as defined by the number of days that patients took at least one dose of the study medication. You can see that the vast majority of patients in the clinical studies achieved 100 percent compliance and virtually everybody was greater than 90 percent compliant. Based on the

very limited amount of patients who had poor compliance, and that is, at least in this slide, less than 90 percent, we did not break this down by the GSS or the PSS score.

DR. GRANT: Also to follow on a different topic, do you have any evidence that your agent is active against subtype C of HIV? I am specifically interested in slide 45 from the sponsor=s presentation. It looks to me like the non-clade B viruses had somewhat less response, or a trend towards less response than the clade B viruses. So, part of my question would be of those 56 non-clade B infections, how many were subtype C? And, in the non-clinical panel there were 18 viruses tested but there was no indication of how many of those 18 were subtype C.

DR. ISAACS: Firstly, as you were alluding to, we did do in vitro analyses against isolates from a variety of different clades and the efficacy, as measured by in vitro IC_{50} was similar regardless of the clade that was measured. I am looking for a specific slide. Could I have slide

468 to preview, please? Thank you.

[Slide]

This slide is actually similar to the slide that you were referring to in the core deck but I am showing it rather than the core deck slide because it actually shows, in addition to the difference in response rates between the raltegravir and the placebo group, on the right-hand side of the graph, which is the forest plot which was present in the less than 400 copy analysisB-this would have been the left forest plot on the three-forest plot graph that you are referring to from the core slide. In addition to the forest plot, you see the actual response rate. You can see, if you look at the bottom two lines looking at clade B and non-clade B viruses, that the actual response rate from the non-clade B viruses is actually very good and that the difference in treatment effect is approximately the same for the clade B viruses, but with the small numbers the 95 percent confidence interval, the lower bound, does cross zero.

We also indicated in our background package that we had full 24-week data and referred to that in the background package with the agreement of the agency. When you actually do this analysis with the full data set with everybody through week 24, the lower bound of the confidence interval actually is greater than zero in that analysis for the non-clade B viruses. So, we do believe that the totality of the data is that raltegravir is effective in all these subgroups.

I think one of the most remarkable things, to my mind, as we look at the data from raltegravir is just how consistent every subgroup analysis that we did-Bjust how consistent the treatment effect was, regardless of the way that we looked at the data, in terms of the efficacy of raltegravir.

DR. GRANT: I may have missed it but were there any subtype C infections in that group of non-clade B virus infections?

DR. ISAACS: I don=t know the answer to that question.

DR. GRANT: Then just one last question,

this to the FDA, I am wondering if there has been a discussion regarding what molecules should be tested in integrase inhibitor development for off-target effects? I noticed in some of the backgrounders that we know that raltegravir does not affect DNA polymerases alpha, gamma and beta but I am wondering if that is the right molecule to be testing. It seems in itself to be off target. Are there host genes involved in strand transfer in immune activation and maturation, for example, that should be in a panel that is tested for integrase inhibitors?

DR. O=REAR: I am Joe O=Rear. I am microbiology team leader in antiviral drugs. We don=t usually ask for a broad number of assessments against different enzymes. The way we usually try to address that question is to have the sponsors look at cytotoxicity and stationary and proliferating cells. So, if the agent doesn=t get into different compartments it is not going to really be a relevant issue so that is the way we try to address that, and I don=t think it was a

concern with this agent. Do you have a follow up?

DR. GRANT: Well, why were DNA polymerases tested with the agent? I am just curious.

DR. O=REAR: Well, the sponsors frequently provide that information. We didn=t ask for it.

DR. GRANT: And the concern I would have would be with immune maturation or maturation of the immune responses which would not necessarily manifest as a cytotoxic phenotype in cell culture.

DR. O=REAR: I think the pharmacologists/ toxicologists usually look at that question. That is not one that we usually address as the virology group. I don=t know if there is somebody who could address that.

DR. PAXTON: Well, in the absence of anybody leaping up to address that, let=s move on to Dr. Hendrix.

DR. HENDRIX: I have a question to come back to the concentration variability. You showed a lot of data, especially in some of the early studies, looking at the flat dose response and there are statements about there being a flat dose

response in the studies. But with all the wide variation, especially with the drug interactions, can you actually show some of the pharmacodynamic analyses? Any measure of concentration versus any of your three or four measures of virologic effect? You know, with tipranavir, to come back to Dr. Haven=s question, the lower 90 percent confidence intervals are around 30 percent. It is more than a threefold reduction from whatever the population means are. So, it would be nice to see just how non-different those are, looking at their antiviral response.

DR. WENNING: I am Larissa Wenning, from the clinical PK/PRODUCT department. If I could show slide 1070?

[Slide]

What I am showing here is a pretty typical PK/PRODUCT analysis using pooled data in treatment-experienced patients from protocol 5, protocol 18 and protocol 19. So, we are looking at data here from all doses in those studies, so 200, 400 and 600 mg data from protocol 5 and then the

400 mg data from protocol 18 and 19.

What we are showing here on the You axis is the percentage of patients with HIV RNA less than 400 copies/mL, and on the X axis we have observed $C_{12\text{-hour}}$ concentrations divided into quartiles. So the very leftmost bar has the 25 percent of patients with the lowest $C_{12\text{-hour}}$ concentrations. The rightmost bar has the upper quartile. And, you can see that there is really not much difference in the percentage of patients with HIV RNA less than 400 by their $C_{12\text{-hour}}$ concentration.

DR. HENDRIX: So, the 8 to 125, how many fall below sort of your means does that represent?

DR. WENNING: Sure. So, the median for this group is about 270 nM so it is half or below.

DR. HENDRIX: So, it is at least half or below half.

DR. WENNING: Right. We did also actually do a separate analysis looking specifically at subjects who had observed $C_{12\text{-hour}}$ concentrations below 33 nM, which is below their in vitro IC_{95} and,

again, there is really no difference there.

DR. HENDRIX: So, those that were below the IC_{95} were the same. They were high 70s and 80.

DR. WENNING: If we could show slide 1071?

DR. HENDRIX: We also want to know what the total number of slides is that you actually have!

[Laughter]

[Slide]

DR. WENNING: What I am showing here is that lower quartile divided out for observed $C_{12\text{-hour}}$ less than 33 nM. It is a small number of patients. It is 16 out of the 332 included in this analysis. Again, it is a small number of patients but there doesn=t appear to be a worse response in those patients compared to the others.

DR. PAXTON: Dr. Feinberg?

DR. FEINBERG: I want to follow up on several comments that have been made about the variability, by Dr. Havens and Dr. Hendrix and whoever else about the variability that has been observed. It is fascinating to me. This is clearly a very active drug, but it is fascinating

to me, the conundrum of how variableB-how all these variable doses produce the same clinical outcome. You know, perhaps we are at the plateau for the dose-response curve. That would account for that.

But I think there are just a number of areas where this touches that leave me with some concerns. First of all, the small, separate study that you did with the UGT1A1 genotypes was interesting but I wonder what the genotypic background and the level of expression of UGT--how that affects the variability of the levels we see because, again, we are all going to be prescribing for specific individuals not for large groups.

The question that was raised about the clade also makes me think that non-clade Bs may be in specific geographic areas and, again, what implication that has for the genetic expression of UGT in those populations. You know, it is clear from the data that it is going to be extremely difficult, if not impossible, to establish clinical cut-offs for raltegravir given the data that we have been shown.

The last piece is, now that I have expressed all these concerns and this is a specific question, I know that the studies were conducted with dosing being done without regard to food. But the trough value, the C_{12}, is 8.5-fold higher when the drug is administered in the fed state. So, although it clearly works without being co-administered with food, I am wondering why we wouldn=t be suggesting or recommending or hoping that people would prescribe it preferentially with food, given all this other variability. I am trying to picture where an individual patient would fit in this kind of floating world where the values are so variable.

DR. IWAMOTO: I will first address the food effect. As you state, in our efficacy studies in Phase 2 and Phase 3 we had conducted the studies without regard to food. And, as you point out, we did perform a definitive food effect study which was performed with a high-fat meal which resulted in an increase in trough concentration. I would like to point out that a high-fat meal is a meal

that is not typically consumed. We did study it because of the extreme effects of the high-fat content. In our Phase 1 program we do also have data with moderate-fat meal administration and we performed a cross-study comparison looking at individuals receiving multiple doses of raltegravir in the fasting state compared with moderate-fat meal administration. May I have slide number 912, please?

[Slide]

What we see here along the X axis are the two groups of individuals being compared, those receiving raltegravir in the fasting state relative to those in the fed state with the moderate-fat meal. Along the You axis is the $C_{12\text{-hour}}$ concentration. We see here that there is not a substantive difference in trough concentration and that food does not reliably increase trough. This then supports our recommendation that raltegravir may be administered without regard to food and then, again, with regard to our efficacy data in Phase 2 and Phase 3 where we have robust efficacy

and raltegravir was dosed without regard to food.

DR. FEINBERG: Although that is a log scale.

DR. HAVENS: Right.

DR. FEINBERG: Could you go back to that slide, please?

DR. IWAMOTO: The GMR in the comparison is 1.4.

DR. FEINBERG: For which?

DR. IWAMOTO: I am sorry, the ratio of fed over fasting. May I address the question of UGT1A1 with regard to variability? In the efficacy studies we did not collect information with regard to UGT1A1 genotypes. I do want to point out that with our atazanavir interaction data where atazanavir does decrease UGT1A1, which is reflective of individuals with decreased UGT1A1 activity, and I believe your question was specifically with regard to safety, if I am not mistaken?

DR. FEINBERG: No, it was sort of broader than that. Ultimately, how that is going to be

expressed in terms of effectiveness and clade differences, resistance development. There are broader implications I believe.

DR. IWAMOTO: Let me defer to Dr. Isaacs to address that.

DR. ISAACS: Maybe I will try and address that question. I think that the issue that you raise is complicated as one thinks about it, but I think the clinical data are not complicated in this regard. In the Phase 3 program raltegravir was given in combination with a wide variety of agents, some of which will raise the level and some which will lower the level of the drug. Both antiretroviral agents and other concomitant therapies, and consistently over every different subgroup analysis that one looks at, the raltegravir benefit was demonstrated. So, with the dose of 400 mg twice daily, given without regard to food, you get an excellent antiretroviral effect across the patient groups that were studied and the safety profile was generally well tolerated and safe.

DR. FEINBERG: No, I understand that. I understand the results of all of those analyses. So, I guess when you think about an individual patient, however, what happens when you have a patient whose UGT genotypic ability to handle the drug is considerably altered and they are on concomitant therapy that would tend to give you the lower end of the raltegravir dose? So, I understand across an entire population this worked out really nicely, but when I see an individual patient how am I going to know whether concomitant therapies and what aspect of their inherited metabolic capacity is going to put them in a corner where everything is altering toward a lower dose? That is why I am asking about, you know, is there value, you know, in knowing that from stored samples in the Phase 3 studies or prospectively in knowing that. Just as we have learned that, you know, B5701 confers a real susceptibility to an adverse reaction to abacavir, you know, should we be looking for a genotypic basis that means we should treat people differently with regard to

raltegravir or other drugs they get plus raltegravir?

DR. ISAACS: The totality of the data lead us to conclude that you don=t need to do that. I do want to make one point, and that is that in situations where UGT1 is not acting as well to polymorphisms as it would in, say, the wild type you would actually expect to see drug levels rise, not fall, and that is exactly what you are doing with atazanavir inhibition of UGT metabolism. The dose-ranging studies, including data from the Phase 3 program in patients who were receiving raltegravir with either atazanavir or tenofovir or both of those drugs did not identify any dose-limiting toxicities nor, for that matter, any dose-related toxicities. So, the selection of the 400 mg dose on the safety side actually gives you quite a bit of flexibility because the increased exposures are covered by clinical experience and would not suggest that a clinically relevant safety issue would arise in the situation that you are discussing.

DR. PAXTON: Miss Swan?

MS. SWAN: Thank you. My first question is for FDA. Do you have any kind of standard that you are working towards in the amount of long-term follow up you would like to see with agents from completely novel classes?

DR. MURRAY: I think we discussed this a little bit at the last advisory committee meeting for miraviroc. I guess that was a little bit different because that has more of kind of a host-related target. But I think, first of all, you have to remember that what is before the committee today is accelerated approval so we are making decisions based on shorter-term viral load data which will be later confirmed by longer-term viral load data, and that also gives you a longer-term safety database as well for traditional approval besides showing durability of the biological response. But I think that with post-marketing commitments we have been looking in the range of three to five years, probably closer to three years, of some long-term safety data, and

resistance and other data for follow up as post-marketing commitments. So, that has kind of been in the range of what we have been asking in later drug development plans.

DR. BIRNKRANT: Then, with regard to the naive population we have been asking for longer-term data, not just 24 weeks.

DR. PAXTON: Dr. Yarchoan?

DR. YARCHOAN: Not to beat a dead horse but just to understand I have a follow-up question on malignancies. Again, part of the issue is that malignancies are common in HIV patients anyway so it may be particularly difficult to see if there is any drug effect in this background. The reported literature is actually very difficult in this field because of the changing rates of the underlying viruses that cause these, and the reported rates for some of these malignancies really vary all over the place. In lymphoma there has been a tenfold difference.

So, I am really trying to understand the data. In the FDA report they talked about that at

database lock for the SUR, there have been 20 subjects with 21 neoplasms, and it looked like there 20 taking the drug and one not taking it. You talk about 10 malignancies in those on drug. So, I am wondering where the additional 10 patients-Bthere is a major discrepancy in that. What group of patients are being included in the FDA analysis. Then, looking at the 20 to 1, what is the denominator of the patients of the 20 and what is the denominator of the patients to 1, and is that statistically significant? I am just assuming that you must have looked at that data at some point.

DR. ISAACS: So, there are lots of different numbers all over the place here.

DR. YARCHOAN: That is my problem.

DR. ISAACS: Let me try and walk through the numbers as I understand them and perhaps Dr. Connelly can comment if I speak incorrectly about her analyses.

So, we looked at essentially three different populations. Before we even start with

the numbers let me just describe the populations we looked at. We looked at the double-blind, placebo-controlled data or the comparator controlled data because it, firstly, enabled us to compare to a comparator group and it also enabled us to determine a relative risk because we had rates for both groups. Secondly, there are two reasons for the major imbalance in exposure rates between raltegravir and the comparator group. That is, one, as Dr. Connelly pointed out earlier, it is because in the Phase 2 studies the randomization was either 1:3 or 1:4 and in the Phase 3 program it was 1:2. But, in addition to that, in the Phase 2 and 3 treatment-experienced studies once you failed you could go on to open-label raltegravir. Particularly in the Phase 2 study where the response rate in the placebo group was less than 20 percent, virtually everybody from the placebo group is actually on raltegravir. Then, in the Phase 3 treatment-experienced studies the response rate in the comparator group was only in the 40 percent range. So, as Dr. Nguyen indicated, a large number

of the patients from the comparator group had gone on to raltegravir as well. So, we have a large amount of open-label experience.

So, the second thing we looked at was if we combine only data from the double-blind raltegravir exposure with the open-label raltegravir exposure, what does that look like. Then, finally, we have experience outside of the clinical program, predominantly in the expanded access environment where we don=t have a good handle on what the amount of time of exposure is at this point. There are over 5,000 people in the expanded access environment, spread over more than 40 different countries and we can=t calculate an exposure rate per patient-year on that. But we looked at those cancers based on reports through serious adverse experience reporting to see whether the patterns were any different from what we had seen previously.

So, those are the three different groups that we are looking at and the primary conclusions were drawn based on the double-blind but the data

from the double-blind plus the open-label for raltegravir are entirely supportive of those analyses, and the expanded access environment just shows the same kinds of cancers and distributions that were seen in the double-blind, which is why I think both Dr. Connelly and I have been focusing on the double-blind period. So, that is a slightly long walk through it but I just want to be clear because we clearly didn=t do a good a job to remove that confusion when we started out.

If you look at the double-blind period, there are essentially three different double-blind periods. There is the double-blind period which was reported in the original drug application and that was ten patients in the raltegravir group and one patient in the comparator group. That patient was in the treatment-naive study in that original submission. So, Dr. Connelly actually showed you an analysis based on all data and an analysis removing the treatment-naive patients. That is why in one case it was 10/1 and in the other case it was 10/0.

I normally just jump at this point to the July 9th cumulative data because it represents an additional six months of follow up or 60 percent greater patient-years of exposure. When you do that you get to 19 patients in the raltegravir group in the double-blind period versus 5 patients in the control group. So, the big change that has taken place between the original filing and the cumulative period is that the number of patients in the placebo group has started to come up. When you look at the data, our interpretation was that it wasn=t so much an issue of the cancers that were occurring in the raltegravir group, it was more an issue that the placebo group seemed to have a smaller number of cases than you would have expected so you have gone from 10/1 with the original filing to 19/5 in the July 9th cumulative analysis based on the double-blind data.

If you look at the July 9th cumulative analysis and you focus just on the raltegravir groups, during the double-blind period there were 2.3 cases per 100 patient-years during the

double-blind period. If you then add in the double-blind plus the open-label cases, there were 26 total patients with cancer between the open-label and the double-blind period in the raltegravir group. The case rate is then still 2.3 per 100 patient-years. So, the rate doesn=t change when you add in all those additional cases.

When you then finally do the relative risk calculation, at that point in time it is 2.3 cases per 100 patient-years in the raltegravir group and 1.9 cases per 100 patient-years in the placebo or comparator group, and that is where the relative risk of 1.2 comes. If you use the double-blind plus open-label for that comparison you get the same relative risk. It is just that the confidence interval is a little bit tighter because you have more data.

To go finally to the analysis that Dr. Connelly also showed, if you use that data set and you say I want to exclude the treatment-naive patients, then you lose 3 patients from the raltegravir group and you lose 1 patient from the

comparator group so that gives you a 16 to 4 ratio. The amount of exposure actually changes at that point because you have taken away quite a lot of exposure from both the raltegravir and the comparator group because that is a Phase 2 study and the median exposure is now over a year in most patients and what you are looking at, I believe, is relative risk that is approximately 1.5, taking into account the patient-years of exposure when you do that. That is consistent with your analyses?

DR. CONNELLY: That is consistent. The other thing I just wanted to point out that may have been confusing is that in the applicant=s slide presentation when they were comparing the original information versus the July update, they presented information at the time of the original NDA submission in April based on the December database lock. When I did a pre and then a post the July update, I used the safety update report data so that also accounts for why, even though we have a before and after, my numbers are slightly higher because I was using a baseline data point

that represented two additional months from the original.

DR. YARCHOAN: Is the data I asked for available? Maybe I missed it but I didn=t hear it. Of the 20 to 1 in your analysis, is the denominator for the 20 available? Is the denominator for the 1 available? And, is a statistical analysis of that available from either the sponsor or the agency?

DR. CONNELLY: So, in my analysis, using that 20 to 1, I did my analysis using that February data, limiting it to the double-blind phase in which there would then be 13 to zero because I excluded the one treatment-naive subject who had a malignancy on the efaverenz arm. So, I wanted to compare what is in the backgrounder. I wanted to compare what I will call a more homogeneous population, meaning all treatment-experienced subjects and not including the treatment-naive because at the time my approach was that the denominator incorporating the treatment-naive studies would potentially dilute a treatment effect

because there was only one malignancy at that point in the treatment-naive subjects. So, I limited it to just the treatment-experienced subjects. Using that definition, the denominator incorporating all doses in protocol 5 and then protocols 18 and 19 in Phase 3 gives you a denominator of 595 and the numerator was 13. Then, the denominator in the placebo would be 282. So, zero over 282. Then, in the interim, between the time that you asked your first question and now, I was given a note saying that this is highly statistically significant, with a p value of less than 0.001.

DR. MURRAY: If I could just comment something on p values for safety data, when we are looking for signals and we don=t have any a priori signal or something that is defined in the protocol ahead of time it is really hard to generate p values. You don=t really know how to adjust for multiple comparisons.

DR. YARCHOAN: I understand.

DR. MURRAY: I just want to say too that sometimes the way that we look at safety is that

something could be highly significant and may not be a signal, something might not be, just a numerical difference, but if it is a temporally related usual drug event, like a rash or a Hy=s Law, we would think that that might be more likely a signal. So, you know, statistical significance helps to kind of pick out some things to look at as kind of hypothesis generating, but just so in general people know why we have trouble with p values for safety evaluation. It is difficult.

DR. YARCHOAN: It is just very hard to get one=s hands around those numbers.

DR. PAXTON: Now we have doctors Havens, Andersen, Glesby, Gordin and Swan. So, Dr. Havens?

DR. HAVENS: What time is lunch?

[Laughter]

DR. PAXTON: Well, that is all up to you now.

DR. HAVENS: Maybe I will wait until after lunch. That was a real question.

[Laughter]

DR. PAXTON: And a very important one.

DR. HAVENS: Because I don=t want to get involved in a question that might involve follow up if we are about to break.

DR. PAXTON: Well, we are actually on schedule. Lunch is on for 12:30. I had originally thought that because we were so far ahead we discussed stopping at noon. I am willing to take the direction of the committee here. We could go to 12:30 as we are scheduled or we could stop at noon and then come back.

DR. HAVENS: I offer no direction; I only want to know.

DR. PAXTON: Yes. Well, we are on the schedule for 12:30.

DR. HAVENS: First I would like to make a comment in support of Dr. Andersen=s earlier issue about whether or not you should expand the population that you suggest this drug is useful for in the context of the conversations that have been occurring about the risk. That is to say, it looks like there is no risk and you tested in a population and it looks good and so you might want

to use it in a broader population. Why, then expanding that is fine but if there is some risk or significant potential risk, then expanding the population without thinking about it is potentially very dangerous. So, when we think about the recommendation that we will give at the end of the day for should this be recommended we need to keep clearly in mind what Dr. Andersen was talking about in terms of do you want this restricted to people who have three-class resistance, which is how these are defined I think, or is it okay to have it be in people who are antiretroviral experienced, which is a different and broader population, given all the concerns about toxicity. So, that wasn=t a question. That was just supportive of Dr. Andersen. Okay?

DR. PAXTON: So noted. You are right, I think it does need to be delineated, exactly what we are talking about, three-class resistance versus just treatment-experienced. So, we will have to deal with that. Do you want to follow up?

DR. HAVENS: Yes, now I have a real

question. It is for the applicant. I am so confused about the kinetics target and I need your help. The backgrounder, which I thought was very nicely written, suggested that the $C_{12\text{-hour}}$ was the important kinetics target of interest and you wanted it to be above 33, and there was pretty wide variability initially with some people who had reasonably higher CIC as given in the backgrounder. But then in your studies you didn=t show that the $C_{12\text{-hour}}$ was associated with outcome. What is associated with outcome? And, how can I understand how to use this drug in my patients based on what kinetics variables? This is important in developing drugs for use in other populations. For example in children you might start with a dose that is low enough to not hurt anybody but if you get a low some sort of kinetics value, that I am asking you to define, you might increase the dose. So, I am asking what is the kinetics target that you are going to use, that I should use, and how did you arrive at that? A perhaps related question-Byou have over a thousand slides, what is

the slide you least want me to ask you for?

[Laughter]

Just do the kinetics one first.

DR. ISAACS: I think it would be unequivocally true that if I knew the answer to your question I would have a much easier time today than I am actually having. We made certain assumptions in developing this drug. This is the first-in-class integrase inhibitor. We had no a priori information as to what was going to be the correct pharmacokinetic target and so we made the assumption that the most conservative thing to do was to try and cover the IC_{95} or the CIC_{95} of the virus for the entire dosing interval, considering that that was conservative and we couldn=t go wrong. When we selected the doses for the Phase 2 dose-ranging studies we didn=t feel it was appropriate to select doses which we thought would be inadequate. So, we selected doses which all were predicted, based on the Phase 1 single-dose and multi-dose pharmacokinetic studies, that the mean trough concentration would exceed the CIC_{95} of

the virus which, at the time that we did the studies, was 33 nM and has subsequently been refined to 31 nM. But for argument=s sake, let=s just talk about 30 nM as a round number.

What we ended up with was efficacy in all the doses we studied, and the totality of the data would lead to the conclusion that we are on the plateau of the dose-response curve but we don=t know how close to the point of inflection we are. We don=t know which parameter is associated with that efficacy. We continue to believe that the most conservative thing to do is to base it on trough concentration, just based on general principles and the imperfect association which has been shown between other antiretroviral drugs and trough concentrations.

But I cannot give you a parameter or a number which we should be setting as a target. For example, in the pediatric program we have set targets which have been based around what has been effective in adults to help us try and sort out, once we get PK in children, how we should proceed

in selecting doses for children.

DR. HAVENS: So, is that going to be the mean that was found in the earlier studies, which was 130, or the mean that was found in the later studies, which was 270B-excuse me, 140 versus 271? The early studies and the later studies had fairly dramatic-Bexcuse me, I shouldn=t use that word. One is 141 and the other one is 271. You can interpret that how you want, but on page 51 of the backgrounder it describes the kinetics of 400 mg BID in study 004 as a C_{min} of 141 compared to the Phase 3 studies which had a C_{min} of 271. Those are different.

DR. ISAACS: Let me just clarify briefly and I can ask my colleague from drug metabolism to come up if necessary.

DR. HAVENS: So, my question to you is which of those $C_{min=s}$ are you taking forward to follow into the next studies?

DR. ISAACS: The 140 nM relates to the monotherapy arm of the treatment-naive study. So, just to remind the committee, because we did not

talk about the treatment-naive study in any great detail today, it was a two-part study in which a small number of patients, 35 patients, were enrolled in a ten-day monotherapy dose-ranging arm, and then after the data was available from those patients the combination therapy arm was started in a much larger number of patients. The number you quote for the treatment-experienced studies reflects the use of raltegravir in combination therapy with the other agents that were present in those combination regimens. I just wanted to clarify where the two different numbers came from. We feel that the 270 nM is more reflective of what is present in the population of people who are getting treated. If you want further clarification on that I can get my colleague from drug metabolism to provide more information.

DR. HAVENS: I would be interested to see. Then, 270 is your target $C_{12\text{-hours}}$.

DR. ISAACS: No--

DR. HAVENS: Oh, I misunderstood. You said going forward that is what you would use as your

target.

DR. WENNING: Just to clarify, for the pediatric study in particular which you asked about, the targets there are based on 400 mg fasted monotherapy doses--

DR. HAVENS: 130.

DR. WENNING: So, it is more like that number. It is based on a combination, I believe, of data from patients in protocol 4 and healthy volunteer data where we have full profiles for the 400 mg fasted dose.

DR. HAVENS: So, then it will be based on a target that is approximately half of the target that was shown to be clinically effective.

DR. WENNING: So, it is a conservative target that is based on how we are measuring PK in the pediatric patients, which is also under relatively controlled conditions.

DR. HENDRIX: Every concentration they measured was effective.

DR. ISAACS: Yes. Can I just make one additional comment? I think we are potentially

confusing here the mean concentration that was achieved and what is an effective concentration. So, we know from the patients who were receiving tipranavir that the mean trough concentration was around the 100 nM point, which was at least threefold in excess of the CIC_{95} of the virus. So, I don=t think that we are saying that 270 nM is a target. We are saying that was the mean trough that was observed in the Phase 3 clinical program. As was just pointed out, all of the doses that we studied were effective. In the Phase 2 dose-ranging studies all of those doses out through 48 weeks showed similar efficacy.

To come back to what I said originally, other than that it would be much easier if I absolutely had a number that I could give you, we don=t know the parameter that is associated and, if it is trough, we don=t know what that trough number is that you have to exceed. The overall data that we have does not demonstrate an association between efficacy outcome and the measured concentrations in the clinical studies.

DR. HAVENS: Did you look at the relationship between kinetics variables and the CIC of the viral isolates, similar to the inhibitory quotient, recognizing that, for example, with lopinavir/ritonavir in treatment-experienced patients the C_{min} or C trough itself does not show a relationship to outcome, whereas the inhibitory quotient shows a relationship to outcome? Did you look at that variable, given that other highly potent agents don=t show a similar kind of non-association between trough but when you take into account the CIC and relate them as the inhibitory quotient you can see a difference?

DR. ISAACS: We did not do that analysis. Let me introduce Dr. Gottensdiene.

DR. GOTTENSDIENE: Hi. Keith Gottensdiene, from the clinical group. You are asking a bunch of very difficult questions.

DR. HAVENS: Yes, but if I am going to use this drug based on this approval these are the kinds of things that I need to know to be able to use it appropriately in my patients.

DR. GOTTENSDIENE: Well, actually, I would probably disagree with that last statement, only because of the way the data turned out. So, in principle I would agree having a target is extremely useful. In practice, what we have shown is that across the whole span of concentrations that we have looked at we have seen the efficacy. Really, from the numbers that Dr. Wenning showed you back down to that bottom quartile of patients who are under the IC_{95}, we continue to see efficacy that goes the whole range of C_{12}. Now, we know that at some point there will be, as Dr. Isaacs pointed out, an inflection point. There is going to be some value below which this drug is not efficacious. So far, we don=t see any signs of that as we move down across the concentration response parameters.

Now, that is a wonderful spot for a drug to be in. You know, in a sense we are in the lucky situation where we seem to have a broad range of concentrations that are both effective and are safe. So, I think Dr. Isaacs is right. We went

into this with the hopes that the PK/PRODUCT analyses would clearly define a parameter that would answer your question. We had hoped that we would be able to say 15 nM trough or 33 nM trough is a value you need to protect or stay away from in individual patients, and make recommendations based upon that. In practice, we are very delighted to see the result that came out, which is that across the whole range of concentrations we see the kind of efficacy we would like to deliver for our individual patients.

Now, we haven=t actually done the individual analysis that you asked related outcome it because we haven=t actually analyzed in the individual patient HIV isolates what the IC_{95} is. But in our in vitro studies the IC_{95s} were remarkably consistent but we can=t actually say that we have explored that type of analysis that you have asked for.

DR. HAVENS: Now, the response--it is all in the efficacy data. It only goes part way because of the design of the study, which is your

drug on top of optimized background. I would refer you to page 9 table 4 of the FDA backgrounder, showing that the placebo group that was naive to enfurvitide and naive to darunavir had an 86 percent outcome of less than 50 copies/mL. So, if we wanted to just look at that we could say what the efficacy was but the design of these studies is very tricky and you get away with a lot which is, for example, the difference between the earlier studies and the later studies, the earlier studies not allowing darunavir and the later studies allowing darunavir. So, it is important in your backgrounder because what is in the OBT is a very important part of understanding the efficacy. When I ask you a specific question about the kinetics and you fall back on efficacy, I fall back on darunavir and enfurvitide and say, you know, you got a lot of efficacy benefit by being in another group.

There is no doubt that this is a great drug, absolutely, and it is very useful for patients who have experienced lots of failure.

That is not the issue. The issue is in trying to understand how to use it in a way that will optimize its efficacy so the patients I use it in are not going towards 70 percent but, rather, I can say if you use it this way it is 90 percent. How much is the UGT1A1 genotype? Fifty bucks probably; maybe 25 by next year. To have these data without looking at the phenotype doesn=t make sense in 2007. You guys want this for a population. I understand that. We need it for a patient.

DR. GOTTENSDIENE: Yes. Dr. Havens, I sympathize with what you are trying to say.

DR. HAVENS: I appreciate your sympathy!

[Laughter]

DR. GOTTENSDIENE: The way to approach some of those questions is to look in subgroups of patients, and what we are trying to do is present a whole variety of subgroups of patients that provide efficacy. It is our impression, it is our feeling and I think the data supports it, that in just about all the subgroups that we looked at one can see a difference between raltegravir and the

comparator. Even in the population that Dr. Andersen brought up with the GSS greater than or equal to zero there are differences that actually had or approached statistical significance. Of course, in that population one would expect that those differences would be smaller because you are correct, in the setting of different kinds of OBT, different background therapy, one would expect raltegravir could add more or less if the patients are effectively treated with other agents. I think that is clear.

I do think you raise some very good questions about trying to understand this and some of the data will come out of additional studies that we are doing. We are continuing to gather data from our different populations. There clearly are also many sources of variability, some of which we have investigated and some of which we have not investigated in detail. In the case of the UGT1A1, we investigated that in a clinical pharmacology Phase 1 trial because we thought it would be much clearer to understand those results since for the

UGT1A1 we were concerned about a safety question, could people who had the *28 have higher levels of the drug?

We particularly looked at the ACU measurement which we thought might be a better representation of the issue of safety, and in that population-BDr. McGowan read off very nicely the C_{12} GMRs, but the AUC GMRs were much smaller, about 1.4. So, we came to the conclusion that if you take the absolute worst case, the *28 homozygous patient, which is known to be a significant impairment in UGT1A1, there is about a 40 percent increase in the AUC overall. So, in a sense we are able to say, just like we do with drug-drug interactions in many of our other analysesB-we are able to say there is some effect there, but the effect is relativelyB-I apologize for saying this--modest, going forward.

So, under the circumstances, we do feel that we have investigated the many different sources that may help. Now, I understand that what you would like to be able to do is to have that

information for all the individual patients in our trials and the PK/PRODUCT analyses were an opportunity and an investigation that we did to try to answer that question. Unfortunately, because of where we were in the dose-response curve, we were not able to answer those questions you specifically asked in the PK/PRODUCT analyses.

DR. PAXTON: There was a lot of sympathy expressed between the sponsor and Dr. Havens. I think, in sympathy for those who are looking forward to lunch, we are going to move forward with the remaining people who have questions. Dr. Andersen, you are up next.

DR. ANDERSEN: Just a quick question potentially to both applicant and also the FDA. Is labeling for pregnancy being considered in the rapid approval? Also, are there plans to investigate pregnancy, especially if this is going to be licensed for a very broad indication for prior treatment?

DR. YUEN: I am Ita Yuen, FDA. I am a pharm/tox reviewer for raltegravir. Usually at

this time, in the labels we are going to classify this drug as category C because of some findings in rats. The drug has been studied in rats for its effect on fertility, embryo development and post- and perinatal developments. The sponsor has done this in rats and rabbits, especially for the development of the so-called segment two where the drug is given during the most sensitive organogenesis period and that is done in two species. They have pharmacokinetic data showing that the drug does pass through placenta and there are fetal exposures. In the rat studies they have basically shown that, except for the increased supernumerary rib which is fairly common, it is classified not as a malformation but as a variation. They have seen that increase of the supernumerary rib and that is dose-related in rats. So, because of this finding, it will be classified as category C. But they don=t have any data on pregnant women.

DR. PAXTON: Thank you. Dr. Glesby?

DR. GLESBY: Thank you. I have a

clarification and a question for the sponsor. I am just trying to understand, in light of I guess the discussion that will take place later about the targeted patient population for this drug in the future, on page 57 of the background information there is table 3. I am just trying to reconcile some of the numbers related to prior use of antiretrovirals. So, these subjects in the Phase 3 trials all had to have resistance to at least one drug in each of the NRTI, NNRTI and PI classes. But if these, in fact, are the lower quartiles for prior use of these drugs for all three of those classes the number is zero. So, is it correct that 25 percent of subjects in each arm did not report use of each of those drug classes?

DR. ISAACS: No. Actually, that is incorrect. The table is somewhat misleading in that regard. Let me just state that all patients entering the study did have resistance to at least one agent in each of the classes of antiretroviral agents available at that time based on genotypic and phenotypic resistance testing at entry into the

study. The zeroes in the table represent a vagary in the way that we asked for background therapy. And, because of concerns about ritanovir boosting, we required that the dose of drugs be present. If the dose of drugs were not present we didn=t count them in that particular table as being there, and it would have been a fairer indication if we had represented the data in a slightly different way. Actually, the agency noticed that and let us know about it about the same time that the backgrounder was being finalized so we didn=t have a chance to fix it.

DR. GLESBY: Thank you for the clarification. My question relates to resistance information on table 9 which is on page 76. There were three subjects who I guess were found to have the 148 and 155 mutation. Is anything known about are those combinations in vitro and the fitness of the virus?

DR. ISAACS: I will ask Dr. Miller from our basic research group to answer that question.

DR. MILLER: So, I have to point out that

the way we did those analyses we used multiple independent PCRs for each patient time point in order to get the best determination of the universe of changes that were present. So, in those cases what we actually observed was that those were likely-Bthese were population sequences but they were mixtures so it is possible actually that those are not on the same virus but actually on different viruses in the population. In support of that, in preclinical studies when we put both of those mutations together those viruses basically don=t grow. In addition, in some other data that we have not submitted to the agency we did some clonal sequencing on some of those patients and, in fact, that bore out our supposition that they were separate virus populations. So, we saw 155 alone, 148 alone, never 155 and 148 together.

DR. GLESBY: Thank you.

DR. PAXTON: Dr. Gordin?

DR. GORDIN: I am trying to look at the area of resistance more from a clinical perspective. In your background information you

gave us on table 5, it looks like about 12-13 percent of people rebounded within 16 weeks. In the slide you showed today you point out there is no association between dose, drug concentration and resistance. You also showed some information that essentially all took their pills. The adherence was extremely high. So, who is rebounding and why? Again, it is kind of getting back to what Judith said earlier. In trying to look at this from a clinical perspective, what are the issues that you would say need to be looked at in terms of who might fail and develop resistance?

DR. ISAACS: The number one issue is building a combination regimen that has more than just raltegravir as the active drug. Other factorsB-so PSS and GSS score of greater than zero were associated with responses. Conversely, therefore, PSS or GSS of zero was more correlated with a likelihood to fail. The other things that were correlated with a likelihood to succeed were lower baseline viral loads and high CD4 cell counts at baseline.

DR. GORDIN: Right, I saw that on slide 51 you showed this morning. Can you give us anymore detail? Are all of these rebounders people with no other drug options with scores of zero, or were there some combinations that looked better or worse than others? I am just trying to be somewhat practical here.

DR. ISAACS: I can=t get down to the level of a specific regimen, but I think that the overall data do strongly support the need for another potent agent. Most of the people who failed, when you go through and you look on an individual patient basis, either had no active agent as measured by PhenosenseGT in their OBT or their only other active agent was potentially a nucleoside. That is not to say that that covers everybody but it covers the majority of the patients that we are talking about.

DR. PAXTON: Miss Swan, I think you are next and then Dr. Feinberg and Dr. Yarchoan.

MS. SWAN: I am just wondering if the sponsor could speculate about why in the

raltegravir groups performance dropped when the PSS was highest. I know the numbers were small but it appeared in 018 and 019. Thank you.

DR. ISAACS: I think that the small variations that you are talking about are-Blet me backtrack a minute. The response rates that you see represent observed failure analyses. The small differences that you see once you get beyond a GSS score of 1 or a PSS score of 1 I don=t think represent anything specific related to the potency of the regimen, and there are other factors that are involved in those but I can=t provide any greater detail on that, unless I misunderstood your question.

MS. SWAN: Well, to be really clear, you had a PSS of greater than or equal to 3. It didn=t look like there was a big difference in performance between the placebo arm and the raltegravir arm, granted that the numbers were small.

DR. ISAACS: Oh, I am sorry. Let me just clarify that I have the exact question. I think the point that you are making is that as you get

more active OBT the difference in activity between the placebo group and the raltegravir group decreases. I am sorry, I completely misunderstood your question previously.

That actually I don=t think is unexpected because the standard of care is to treat patients with combination regimens involving two or three active drugs. So, when you actually are getting the placebo group with PSS or GSS scores of 2 or above you are actually giving them presumably a fairly therapeutic regimen. In general though, it was of interest that even in those situations the raltegravir arm did perform better than the placebo arm, albeit the treatment difference was much, much smaller, and I think the overall trend just speaks to the potency that raltegravir adds to the regimen. But it is not unexpected with GSS or PSS scores of 2 or greater that the background regimen would be effective. You also saw that in the breakdown of the enfurvitide and darunavir analysis that we showed. When patients were getting enfurvitide and darunavir together in the placebo

group they were having a response rate which was almost as good but not as good as the raltegravir plus darunavir plus enfurvitide patients. So, the totality of this speaks to the general principle of treating HIV patients, which is that you need to have two or three really potent drugs in the regimen to get the best response. Does that answer your question?

MS. SWAN: And I think the numbers just get too small if I was going to say, okay, who had a PSS of 3 and who got darunavir and who got enfurvitide but, yes, thank you.

DR. PAXTON: I think in the interest of moving forward we will go to Dr. Feinberg.

DR. FEINBERG: I would like to follow up with another question about resistance. You know, I am mindful of the data that were provided in the backgrounder. In the FDA=s presentation there was a comment made about the patients in the protocols for the three-class resistant patients and that resistance was detected as early as day 27. I am wondering if you have data about how fast

resistance appeared in general in both the treatment-experienced and the naive patients. For the experienced patients I know that the analysis showed that a PSS and GSS of zero clearly were factors in resistance, but resistance developed in patients with higher genotypic and phenotypic susceptibility score so there are issues around how fast resistance occurs and then, of course, the corollary issue, which maybe isn=t totally your problem, is that there is apparently cross-resistance with raltegravir as well.

DR. MILLER: You have raised a number of issues. I will try and take them one at a time. If I miss one I will come back to it. So, let me start with the question about kinetics of resistance. I think the important way to think about this is that really the kinetics of resistance mirror the kinetics of virologic failure because essentially resistance leads to virologic failure. So, when we think about that really it is best monitored that way.

We have not yet had a chance to collect a

lot of longitudinal resistance data. We are in the process of doing that right now. But we have, by and large, single determinations near the point of virologic failure. You know, if we were to show you the kinetics of the accumulation of 155 or 148 it would have that inherent bias in it that it was just when we looked.

Let me speak specifically to the one question you asked about early resistance and the effects of optimized background therapy, and so forth. In this patient population it gets very complicated very quickly because there are so many different regimens. But let me just show you and example of a patient who rebounded early that can maybe put this in perspective. Can I have 1634, please?

[Laughter]

DR. FEINBERG: I won the prize!

DR. HAVENS: You got the highest number!

DR. MILLER: It is still early!

[Slide]

Here is just one example in protocol 18.

I have to emphasize here that we also have partial resistance data. This is something that is ongoing. We had a resistance cut-off date to meet the filing deadlines. But of the 20 genotype virologic failures in protocol 18, 19 were rebounders and one was a non-responder. This is actually an example of a patient where we detected resistance pretty early. So, if you look at the bottom there, the overall susceptibility score, both the PSS and the GSS were zero for this patient at entry. This patient was resistant to saquinavir, fosamprenavir, tenofovir and FTC so it was a person who was on functional monotherapy. This patient did develop resistance; did not respond well to raltegravir therapy, as might be predicted. When we looked at four weeks, which was the earliest time which is about 27 days that we heard in the agency=s presentation, we saw evidence of emergence of a resistance mutation at position 143.

But I think what is really important now is this second bit of data that the agency has not

yet seen, but in some of the longitudinal sequencing that we are doing it is clear that resistance in this patient continued to evolve so that when we looked at 18 weeks later, in addition to the mutation at 143, we also saw mutations at two other positions, 97 and 230, which we believe are associated with resistance. So, despite the non-response it looks like the raltegravir continued to exert some selective pressure and caused the virus to have to bring in multiple mutations to develop high-level resistance. Did I answer all of your questions?

DR. FEINBERG: Then what about the five virologic failures in the naive study where one was a genotypically wild type? One actually had an interesting pattern that was raltegravir resistant and had a K65R and didn=t have an M184V which seemed very odd to me. How fast does resistance come up in these naive patients?

DR. MILLER: The simplest thing might be to show you a couple of examples of virologic curves that could get to your question. Could I look at