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**4th IAS Conference on
HIV Pathogenesis, Treatment and Prevention
Clinical Trials ART
International AIDS Society and
Australasian Society for HIV Medicine
July 24, 2007**

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[START RECORDING]

CHRISTINE KATLAMA, M.D.: Can you take a seat? I'm sure we'll start soon. So, my name is Christine Katlama, I'm from the University Pitie-Salpetriere, and I have the very great honor and the pleasure to chair this morning's session on ART with Jose Arribas [inaudible] co-chair [inaudible] session. So, we will have a terrific program with a lot of new data on new drugs, and we hope you will enjoy the session.

So, you have the sheets here. There is two microphones. Every speaker will have 12 minutes to speak, and you have three minutes for discussion. So, the first speaker is Dr. Valdez-Madruga on behalf of the TITAN Group, and he will talk about the comparison 48-week efficacy data on darunavir compared to ritonavir.

JOSE VALDEZ-MADRUGA, M.D.: Good morning. It's a pleasure to be here in Sydney. Today I'll present data from [inaudible] trial. It's a comparison between the two [inaudible] inhibitors, darunavir versus ritonavir in treatment experienced lopinavir naive patients.

This trial is a randomized, controlled trial with [inaudible] six weeks and [inaudible] at week 48. Inclusion criteria. Patients need to be treated experienced [inaudible] with viral load about 1,000 [inaudible] per milliliter, stable HART for 12 weeks or there could be [inaudible] treatment

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interruption for four weeks or more. A total of 785 patients were screened in this 595 patients were randomized and treated with either darunavir 600 milligrams plus ritonavir 100 milligrams bid or with lopinavir 400 milligrams plus ritonavir 100 milligrams bid. Both treatment arms with [inaudible] composed of two or three from approved NRTIs [inaudible]. [Inaudible] was disallowed in this trial. The primary end point of this study was to achieve viral load below 400 copies [misspelled?]. In the primary [inaudible] demonstrates no inferiority confirmed by the load below 400 [misspelled?] [inaudible] with darunavir versus ritonavir at week 48. As a secondary objective, was superiority of darunavir over ritonavir. All the secondary objectives was to evaluate viral load below 50 copies [misspelled?] changing for the [inaudible] and also evaluate efficacy safety and tolerability over nine six weeks.

Baseline [inaudible]. Both treatment arms were well balanced across demographic, disease [inaudible] and treatment history. Patients at an average age of 41 years, mean viral baseline viral load 4.3 logs and median CD4 cell count for 252 cells. A total of 22-percent of patients were on the [inaudible] treatment option and 32 were PI naive at the time of baseline and patients were well balanced according to baseline resistance characterizations.

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In this slide, you see a proportion of patients remain in the trial. As you can see here for most categories most treatment arms were well balanced. The exception was to illogical failure that most patients in the lopinavir arm presented virologic failure than the ritonavir arm. In patients who discontinued the trial, we have [inaudible] both treatment arms. The results of the trial proportion of patients who [inaudible] viral load below 400 copies [misspelled?] at week 48. As you can see here, 77-percent of patients in the darunavir arm achieved viral load below 400 copies [misspelled?]. [Inaudible] 6- to 7-percent of patients achieved viral load below 400 copies [misspelled?] at week 48 and this difference was of statistical significance.

This graph we see the difference between both treatment arms according to viral load below 400 copies [misspelled?] at week 48. As you can see here, the mean difference was 10-percent with confidence interval from two to 17. To establish no inferiority, we need to look at [inaudible] patients' population. As you can see here, the mean difference in the [inaudible] population was [inaudible] with confidence interval from two to 16. In this lower end of the confidence interval, two is about the [inaudible] cutoff for non-inferiority. Then it proves that darunavir was no inferior than lopinavir. To establish this superiority, we need to look at the ITT

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population. The ITT population the mean difference between both treatment arms was 10-percent with confidence intervals from two to 17. If this number, this lowering of the confidence interval is above this zero, the point that the two drugs were equal [misspelled?], it proves that darunavir was not inferior, but it weigh superior to the ritonavir. Viral load below 50 copies [misspelled?] [inaudible]. Again, you see that more patients in the darunavir arm 71-percent of patients versus 6-percent of patients achieved viral load below 50 copies [misspelled?] at week 48. This difference was again statistical significance.

This table here we see that we analyze the subgroup according to baseline lopinavir [inaudible]. When we exclude patients with lopinavir [inaudible] above 40, the mean difference between both treatment arms was 10 and this difference was similar to the overall population that was 11. This difference was highly statistical significant for no inferiority and also significant for superiority. Lopinavir [inaudible] when take the patients ritonavir [inaudible] all below ten we see the mean difference between the both treatment arms was seven, 7-percent. This difference was again statistical significant for no inferiority, but borderline significance for superiority.

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The improvement in CD4 cell count was very similar between both treatment arms. The median change in CD4 cell count was 88 cells in the darunavir arm versus 81 cells in the lopinavir arm. This difference was very similar. Virological failure. Virological failure in this trial defined that if patients who never achieved viral load below 400 copies [misspelled?] and it consisted of responders and no responders. Responders are patients who achieved viral load below 400, sorry, no responders are patients who never achieved viral load below 400 and rebounders are patients who had achieved viral load below 400 and rebounded to viral load above 400. As you can see in this [inaudible], more patients in the lopinavir arm presented virological failure than in the darunavir arm. This difference was two-fold higher in the lopinavir arm. Being more conservative and excluding patients with lopinavir for a change greater than ten, we again see that more patients in the lopinavir arm presented virological failure than in the darunavir arm. The virological failure was more frequent in the lopinavir arm. The development of primary PI, PI mutations in the [inaudible] resistance-associated mutations were more frequent in the lopinavir arm than darunavir arm. Again, when exclude patients with lopinavir change above 10 most patients in the lopinavir arm had [inaudible] primary PI mutations in the [inaudible] than in the darunavir arm.

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The most common adverse event with incidence greater than ten you can see here that diarrhea was the most common adverse event and it was more frequent in the lopinavir arm than in the darunavir arm. Another important adverse event was thrush [misspelled?] and thrush [misspelled?] was more frequent in the darunavir arm, but no grade four thrush [misspelled?] has appeared in only two cases of thrush [misspelled?] led to discontinuation of the trial and one of these [inaudible] was taking [inaudible] in the background. The other adverse events were very similar between both treatment arms. When we look at the adverse events with grade two to four, moderate to severe, possibly related to the third medication. If incidence above 2-percent, again, diarrhea was the most common adverse event and the incidence of diarrhea was twice in the lopinavir arm than in the darunavir arm. Nausea, the second most common adverse event, was similar between both treatment arms and thrush [misspelled?] was most common in the darunavir arm.

Rated two to four laboratory abnormalities with an incidence greater than 2-percent. As you can see here in this table, both treatment arms presented with similar incidence of laboratory abnormalities.

In conclusion, this treatment experience lopinavir population, darunavir was not inferior, but biologically superior to lopinavir. Darunavir was safe and well tolerated

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and darunavir provided better protection of the NATRI [misspelled?] in the PI classes [inaudible] failure versus lopinavir. And finally, I would like to thank the patients and their families for their participation in the trial. I would like to thank the TITAN team especially [inaudible]. And I would like to thank the co-investigators and the investigators that are listed here. I would like to thank my clinical team, and I would like to thank [inaudible] for support in the trial and thank you for your attention.

[Applause]

CHRISTINE KATLAMA, M.D.: Thank you very much, Dr. Valdez, for this excellent data. So, the speaker is now open for discussion. Again, you have two microphones over here and it's perfect they get a number. So, microphone four. The [inaudible] and the number. So, the two and the four.

JAMES WILLIAMS: Thank you. James Williams from the States. Thank you for the information. Just a quick question, is it accurate to say that before six mutations [inaudible] seems to perform equally to Kaletra but after six mutations [inaudible] looks to be a good option to use after Kaletra?

MALE SPEAKER: Yes, so we done, as you can imagine—
[interposing]

CHRISTINE KATLAMA, M.D.: Can you identify yourself?

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DIEGO MORALES: Yes, sorry. This is Diego Morales from [inaudible]. I will answer for Jose because it's kind of a technical question. So, as you can imagine, we've done a lot of additional analysis. We have looked at, we have looked at patients with a full change of less than ten for lopinavir and who had one, one primary PI mutations and there's a statistical significant difference between darunavir and lopinavir in patients where lopinavir had a full change less than ten and only had one primary PI mutations. So it's not driven by six mutations. There's a difference with many less mutations than six.

CHRISTINE KATLAMA, M.D.: Okay. Microphone two, a question to Dr. Valdez?

KEITH CRAWFORD: Yes, Keith Crawford, Howard University, Washington, D.C. Question regarding the rash. Did you screen your patients for history of sulfa allergy before enrolling them in the study?

JOSE VALDEZ-MADRUGA, M.D.: [Inaudible] all kind of disease problems.

MALE SPEAKER: But the question is regarding sulfa allergy. Darunavir having sulfa [inaudible] causing potential for allergic reactions? That could be a cause of the rash if they had a history of sulfa allergies.

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MALE SPEAKER: Sabrina, who works for TevaTech
[misspelled?] will answer this question. [Laughter]

FEMALE SPEAKER: If I can have the microphone so I'm
Sabrina [inaudible] from TevaTech [misspelled?]. So, we looked
at the sulfa allergy prior to start treatment and so the
rashes, there were just two cases that occurred in the
darunavir arm. So, we looked at those data and there was
really no difference and no threat to the [inaudible]. You
have [inaudible] sulfa allergy.

CHRISTINE KATLAMA, M.D.: Okay. Thank you very much.
I think we ought to move to the next presentation. Thank you
very much. [Applause]

So the next presentation will be given by Dr. Gulick,
and it's on the [inaudible] Group of ACTG 5211. So, Dr.
Gulick, it's your turn.

ROY GULICK, M.D., M.P.H.: Thanks, Christine. ACTG
5211 is a phase II study of the vicriviroc in treatment-
experienced patients. I'm pleased to present today the 48-week
results on behalf of the ACTG 5211 protocol team. Our study
objective was to evaluate the safety, tolerability and anti-
retroviral activity of vicriviroc containing regimen. We
enrolled patients who are ART experienced who were failing
their current regimen as evidence by a viral load level of at
least 5,000 copies per mil on a ritonavir containing regimen.

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All patients had a documented R-5 phenotype using the Trofile assay that we stratified at enrollment by both enfuvirtide use and a baseline CD4 count less than or at least 50 cells per micro liter. This slide shows the study design. So, patients entered screening while taking their failing ART regimen. During screening, they underwent genotypic and phenotypic resistance testing as well as tropism testing. At study entry, they were randomized to one of four study arms. They added to their failing regimen either placebo or vicriviroc at one of three doses; five, 10 or 15 milligrams once daily.

They continued that regimen through day 14 and then at day 14 based on the results of resistance testing and the treatment history, optimized their background regimen. Because of the timing of this study, there was not darunavir or tipranavir available for the optimized background regimen. At that point, they continued the randomized therapy plus the optimized regimen through 48 weeks of the study. Access to vicriviroc was provided in a separate rollover study for any patient who completed ACTG 5211. All regimens containing ritonavir both the failing regimen and the optimized regimen. We defined virologic failure as a confirmed less than one log decrease in viral load level from baseline after at least 16 weeks of the study. We also included a crossover option to

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people who experienced virologic failure that they could receive vicriviroc or could increase the dose of vicriviroc.

We enrolled 118 subjects with the median age of 46, represented 92-percent men and 8-percent women. One-third non-whites and two-thirds whites were enrolled. One third were enfuvirtide experienced. The median viral load level on the study was about 36,000 copies per mil at baseline and the CD4 cell count 146 cells per micro liter. As required by the protocol, 100-percent of patients had R5 virus at screening. In terms of disposition through the 48 weeks of the study, study treatment was discontinued early by 82-percent of the placebo arm, 30-percent of the 10-milligram arm and 37-percent of the 15-milligram arm. I neglected to say that the study monitoring committee, an independent group, closed the five-milligram arm early because of suggestion of inferior virologic activity in that arm. Most of the results I will present will focus on the other three treatment arms.

In terms of virologic failure through 48 weeks, 86-percent on the placebo arm experienced virologic failure compared to 27-percent on the 10-milligram arm and 33-percent on the 15-milligram arm. This slide shows the primary efficacy end point on the study, which is the median change in HIV RNA from baseline and this is using an attempt to treat analysis. As you can see, both the 10-milligram arm shown in green and

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the 15-milligram arm shown in light blue produce a potent decrease in viral load level on the order of about two logs, which was durable through the end of 48 weeks. At the end of 48 weeks, the 15-milligram arm was 1.4 logs below baseline and the 10-milligram arm 1.9 logs below baseline level.

This slides shown the proportion in each of three treatment groups who achieved a viral load level less than 50 copies per mil over the course of the study. Once again you can see that the two vicriviroc arms produce more patients reduced to less than 50 copies at the end of 48 weeks so approximately 30- to 40-percent of patients in the vicriviroc groups are suppressed below 50 and that compares with only 10-percent in the placebo group.

CD4 cell counts increased notably in both vicriviroc groups, and you can see by the end of 48 weeks about 100 to 130 median rise above baseline for the vicriviroc patients. We looked at a subgroup analysis based on virologic response in the two vicriviroc groups, 10 and 15 milligrams, by enfuvirtide use. I would like to remind you enfuvirtide use was not randomized on this study. It was chosen by patients and their providers. The largest decrease in viral load level shown for you here with a mean decrease over two logs, the bar represents the median increase and the 25th and 75th quartiles. The whiskers [misspelled?] represent the range of responses, but

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what you can see is that the 12 patients who took vicriviroc were enfuvirtide naive and added enfuvirtide as part of their background regimen had the greatest virologic response again over two log mean decrease. That's similar to the 29 patients who took vicriviroc, but never used enfuvirtide either prior to the study or as part of their background regimen. You can see about a 1.5 log mean decrease. The least response was seen in the 19 patients who took vicriviroc but had had enfuvirtide experience, and you can see about just under a log response in that group. Again, caution interpreting these. These are not randomized groups.

In terms of tropism, again, per protocol, 100 patients, 100-percent of patients entered the study with R-5 virus. However, at the time of study entry, which was prior to receiving study drug, 86-percent continued with R-5 virus, 10-percent had changed their tropism to a dual or mixed phenotype and an additional four patients had a missing result. On study treatment of the 106 patients at study entry with either R-5 or missing tropism results, a total of 18 subjects changed tropism over the course of the study. Three on the placebo arm, two following crossover to vicriviroc following virologic failure, and 15 on the three vicriviroc arms. Eight in the five-milligram arm, four in the 10 milligram and three in the 15-milligram arm.

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Of 26 subjects with R5 virus at study entry on vicriviroc who experienced virologic failure, nine or 35-percent, had dual mixed or X-4 virus. We undertook several post hoc evaluations to try to relate tropism with virologic response. Here's one look at that. This graph shows the time to virologic failure in patients at study entry, ten who had dual or mixed virus shown in yellow and compared that with the 80 who continued to have R5 virus documented by the tropism assay. Recall that our definition of virologic failure could not occur before 16 weeks of study. There is a shorter time to failure in the dual mixed group compared with the R5 group. However, note that the numbers are small and this does not reach statistical significance.

We were also interested in what occurs after tropism change and people receiving vicriviroc in terms of viral load levels and CD4 responses. What we have done here is to look at the 23 patients who had a tropism change set the change at the time point zero and then described what happened to viral load levels and CD4 cell counts over time. Note that there's a different length of follow up because tropism changes occurred at different time points during the study for the 23 patients, but I think what you can see viral load level in yellow really doesn't change after tropism change and CD4 cell count remains relatively stable for up to 48 weeks after tropism change

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although again I would caution that the numbers are smaller on the right hand side of the figure.

In terms of adverse events, there was no significant difference for grade three or four adverse events including signs and symptoms and laboratory abnormalities among the four study arms. No seizures were reported over the 48 weeks of the study. Malignancies we have reported that eight subjects randomized to vicriviroc either through the 48 weeks of the study or in a conservative approach we also include any malignancy, which occurred on the rollover study. We previously reported six of these at week 24 and that included two non-Hodgkin's lymphoma to Hodgkin's lymphoma when gastric adenocarcinoma and a squamous cell carcinoma. An additional two malignancies occurred since that time. A basal cell carcinoma in the 10 milligram group and a recurrence of Cappa C sarcoma in a patient randomized five-milligrams. In addition, two subjects randomized to placebo-developed squamous cell carcinoma. We previously reported both of these patients. One of the two patients briefly received vicriviroc at a dose of 10 milligrams.

In conclusion, ACTG 5211 shows that in treatment-experienced patients following optimization of the background anti-retroviral regimen that vicriviroc at a dose of either ten or 15 milligrams when combined with ritonavir demonstrated

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sustained, durable anti-retroviral activity over 48 weeks. We also show that co-receptor change was documented in about a third of patients who were taking vicriviroc at the time of virologic failure. Vicriviroc was generally well tolerated on this study. The relationship of vicriviroc to malignancy remains uncertain really because of the small sample size of this study. Longer-term follow up of these patients will continue through a total of five years.

I would like to acknowledge the members of the ACTG 5211 protocol team, my co-chairs, Dan Kariskus [misspelled?] and Charlie Flexnor [misspelled?], our statisticians at the Harvard School of Public Health, and our Dades Medical Officer, Katie Godfrey. In addition, team investigators listed here. Many of whom are in the audience and other important members of the ACTG 5211 protocol team. I would also like to acknowledge the pharmaceutical supporter, Schering-Plough Research Institute. Wayne Greves and Lisa Dunkul [misspelled?] being part of the team and Owen Cokley [misspelled?] from Monogram Biosciences and the study sponsor, the Division of AIDS through the AIDS Clinical Trial Group, NIAID at NIH. Lastly, the 25 ACTG study sites who contributed patients to the study and followed them and finally and very importantly, the study participants themselves. Thank you.

[Applause]

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CHRISTINE KATLAMA, M.D.: Thank you very much for your very clear presentation. So, now it's open for discussion. Microphone two.

FRANK REIM: Frank Reim [misspelled?] from Minneapolis [inaudible]. I'm interested in the comparison of the plasma levels in your study and the naive trial. Recall in a naive trial the drug didn't perform quite as well and was unboosted. Dosing was five times the dose, however, and I'm just wondering what the plasma levels are boosted compared to unboosted.

ROY GULICK, M.D., M.P.H.: The question was Frank noted that the doses that we used on 5211 were lower than what was used in the naive study that used vicriviroc, which was sponsored by Schering. In our study, we required all patients to be on ritonavir. That enhances the plasma levels of vicriviroc and the doses in this study were actually chosen to mirror the concentrations achieved with unboosted vicriviroc as used in the Schering study. The other comment you made was about the viral load level at baseline. I'll just remind you that this is a study of treatment-experienced patients who were failing their current regimen. The baseline viral load at the time of study entry here was about 36,000 copies. That's certainly less than it would be on a treatment naive study.

FEMALE SPEAKER: [Inaudible]. When you showed the data concerning this load and viral load and CD4 count after the

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shift in the tropism, was there, did they change treatments if they were on treatment failure or were they kept on vicriviroc?

ROY GULICK, M.D., M.P.H.: Thanks for bringing up that point. It's actually a mixture of approaches in that study group. Early on in the protocol we required that patients discontinue the study drug vicriviroc following a tropism shift, but with increasing information we amended the protocol to allow the patient and their provider to assess whether they were continuing to have a virological and immunologic response and most of the patients were able to continue vicriviroc. This slide I showed was actually a mixture. It's an attempt to treat. So many different strategies were employed. Some patients ended up discontinuing vicriviroc. Others continued it for the full course.

CHRISTINE KATLAMA, M.D.: Microphone two?

MALE SPEAKER: Bolan, Los Angeles. Can you further characterize that, I think it was 14-percent of folks who switched their tropism before they actually started taking the drug? Where they, what was their treatment before they did that? I mean were they on treatment or were they off treatment or what?

ROY GULICK, M.D., M.P.H.: So, again, all patients were required to be on ritonavir containing regimen at the time of screening for the study, and they had to have R5 virus at

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screening. We did another tropism assay at the time of study entry. That was prior to any patient receiving the study drug and the number was 10-percent of the population switched their tropism from R5 to a dual or mixed phenotype.

MALE SPEAKER: Could you explain that slide [inaudible] that said I think viral failure based on baseline tropism?

ROY GULICK, M.D., M.P.H.: Right. So we are looking at the same population I just mentioned. So everyone had R5 at baseline, but 10-percent of the people had switched their tropism at the time of study entry again prior to receiving vicriviroc. We were interested in how those two groups, those two subsets, and again I would caution people this was a post hoc analysis, but we were interested in what their time to virologic failure would be. So, in the yellow line where the ten patients who had dual or mixed phenotype at the time of study entry and the remainder were the 80 patients who had R5 phenotype. All 90 of those patients received vicriviroc. What we should have seen was that the time to virologic failure was faster in people who had dual or mixed virus, but because of small numbers over the time it didn't reach statistical significance.

MALE SPEAKER: Thanks.

CHRISTINE KATLAMA, M.D.: Thank you very much.

[Applause]

So, after the PI, we are moving now to the integrase inhibitors, and we welcome Mr. Murray from [inaudible] they are mixed Australian-American team to talk about viral decay of raltegravir.

JOHN M. MURRAY, B.SC.(HONS), M.SC., PH.D.: Thank you. So, raltegravir belongs to the new class of [inaudible] integrase inhibitors. It prevents incorporation of the completed HIV DNA genome into the host cell genome. It acts after reverse transcription and so it targets the novel process of HIV one log cycle.

There's also a different process to [inaudible] inhibitors that reduce productive, reduce infectious virus from previously infected cells. So, I have some results in phase II studies for individuals with multiple class drug resistance. Patients on the raltegravir arm combined with optimized background therapy suppress virus faster than those without [inaudible]. So, these are individuals with multiple class resistance so it shouldn't be, it should be expected that perhaps raltegravir belonging to a new class of drugs may prove superior in that instance. In the cases of individuals that are anti-retroviral naive, we may not expect such an improvement, and we wouldn't expect difference in viral decay dynamics for anti-retroviral naive patients under raltegravir.

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Typically anti-retroviral therapy, [inaudible] RNA and [inaudible] experiences multi-phasic decay. The first phase with half, about one and a half days, tracks the loss of productively infected cells as these are lost and not replaced due to prevention of infection. After about a week there's a slower second phase decay with a half-life of about 14 days and this is believed to track the production of virus from long-lived infected cells. Afterwards under around about 50-copy assay there's a third phase where the origins of this are unclear.

So, protocol 004 part one of that looked at ten days of monotherapy with raltegravir in anti-retroviral naive patients. So this was the dosing and effects of raltegravir. There are four doses, 100, 200, 400 and 600 milligrams versus placebo. These are plots of individual patients over that ten days. So, there was no difference in the, they all experienced multi-phasing, sorry, they all experienced mono-phasic decay with a median 2.2 log decrease and with no significant difference between the four dosage groups. So, all groups were significantly, sorry, all groups with similar with a 1.2 day half-life over all raltegravir patients.

Part two of this study looked at combination therapy of raltegravir with tenofovir and lamivudine versus another arm with the [inaudible] same two drugs. Once again with the four

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dosage groups. Approximately 40 in each group as well as in the [inaudible] group patients still treatment naive. So they follow these patients over 48 weeks of therapy. So, each of the raltegravir groups achieved undetectable HRV RNA [misspelled?] at 50 copy assay limit. Faster than the [inaudible] group. So, at day 15 – so the first time point after the start of therapy, at least 30-percent of individuals in the [inaudible] groups, were below the 50 copy limit whereas only 11-percent for those individuals on the [inaudible] arm. Comparisons of each of the raltegravir groups against the [inaudible] arm were significantly different so with a P-value of 0.047. At day 29 the difference was even more discernible with at least 55-percent of individuals in the raltegravir dosage groups being below 50 copy assay with less than a quarter for the [inaudible] arm with a P-value for each of the comparisons of raltegravir against [inaudible] at most 0.003. [Inaudible] 112 some of the raltegravir groups were similar to the [inaudible] arm, but by day 168 there's no difference between the raltegravir and the [inaudible].

So, we combined all patients in the raltegravir groups, and we see the fast initial decrease in their viral load. So, these are looking at medians in the [inaudible] ranges and confidence intervals for these and so the comparison of the

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raltegravir versus the [inaudible] shows the loss, decrease in the [inaudible] compared to the [inaudible] arm.

We can compare these results to results already published about anti-retroviral regimens against treatment naive individuals. So, these are results from Kariska's [misspelled?] looking at first and second phase decay for individuals on the three drugs of [inaudible] arm, four drugs of [inaudible] arm and a triple NRTR regimen producing similar dynamics. The three drug [inaudible] arm from this protocol was consistent with those results. The raltegravir arm was significantly lower than this in the second phase by all levels.

So, under raltegravir [inaudible] levels were 70-percent lower than for the [inaudible] arm and this was highly significant. On the other hand there was no significant difference between the slopes of all decay in the second phase. However, these data means that the theories about second phase viral loads are inconsistent with this. So if raltegravir acts solely as integrase inhibitor then it should not affect viral production from cells that have HIV already integrated into the DNA. So, we should not see, therefore, a difference between raltegravir and the [inaudible] arms if second phase virus was produced from long-lived infected cells.

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Similarly some of the other therapies from second phase virus production are inconsistent including disassociation of virus reduction are inconsistent including disassociation of virus from follicular dendritic cells and down regulation of cytotoxic lymphocyte response. There are some other theories that we were interested in investigating, however. So to investigate these, we constructed some mathematical models. We constructed free models. This first one is a variation of the original therapy that the virus comes from long-lived infected cells. However, so, instead of the virus being produced directly from those cells, we had it provided new rounds of productive infection where the virus then came from the new productively infected cells. We still needed the incorporation of long-lived infected cells in this to provide the slow dynamic we see in second phase viral levels. Here we hypothesize that raltegravir was more effective at inhibiting these new rounds of productive infection.

The second model assumed that there was a pool of lightly infected cells with [inaudible] DNA that was completely reverse transcribed but unintegrated and that the second phase viral level virus arose from conductively infected cells that were converted from this latent form to an integrated form and they produced the virus seen at second phase viral levels and in this case raltegravir inhibited the incorporation of the

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completed HIV DNA gene, genome, that was unintegrated into the integrated part for the productively infected cells.

The third model assumed that raltegravir penetrated sanctuary site better than other drugs, and therefore, limited the output of virus from the source. So, compare simulations of each of these models against data from the monotherapy part of the trial. So that provided the first phase data. From the combination therapy part for raltegravir and the combination therapy part for the [inaudible] arms. So, the raltegravir simulations are solid lines whereas the [inaudible] arm is represented by the dash lines. So, the first few models were consistent with the data whereas the third model did not reproduce the data as well.

So, model one assumes that second phase virus originates from productively infected cells that have been infected from long-lived infected cells and raltegravir inhibits this new round of infection more effectively than other drugs. The second model assumes that second-phase virus originates from activation of lightly infected cells that convert to productively infected cells with integrated virus. In this case, raltegravir inhibits integration, which is a process that would not be affected by the reverse transcriptase inhibitors or protease inhibitors.

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So in conclusion, we find that raltegravir is a potent antiretroviral drug from the new class of HIV integrase inhibitors. It reduces second phase viral levels by 70-percent more than current regimens. That is inconsistent with theories that second phase virus originates from long lived infected cells, on the other hand, it does have the possibility from being through new infection from long lived infected cells or from activation of lately infected cells with unintegrated HIV DNA. On either occasion raltegravir is a very potent new drug. Thank you. [Applause]

CHRISTINE KATLAMA, M.D.: Thank you for this excellent, very precise communication. Discussion? Microphone two.

YANSEN MENSEN: Yansen Mensen [misspelled?] from Hamburg, Germany. Did you have a chance to look at profile DNA DK?

JOHN M. MURRAY, B.S.C.(HONS), M.S.C., Ph.D.: No, that wasn't available, I am afraid.

YANSEN MENSEN: And the chance to look at the LTR, two LTR circles, no?

JOHN M. MURRAY, B.S.C.(HONS), M.S.C., Ph.D.: No.

YANSEN MENSEN: Okay.

CHRISTINE KATLAMA, M.D.: That's all? So [inaudible] trial a clinical question. Apart from thinking about the pathogenesis, what will you think makes a big difference of

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these difference, what about the penetration and the other reason why. Do you have any idea of these different penetration or different action is also true CSF in [inaudible]?

JOHN M. MURRAY, B.S.C.(HONS), M.S.C., Ph.D.: We don't have any data on that, but the modeling of that aspect of penetration into different sanctuary sites was not as good at reproducing the data.

CHRISTINE KATLAMA, M.D.: Okay. So it's mostly for plasma effects?

JOHN M. MURRAY, B.S.C.(HONS), M.S.C., Ph.D.: Yes.

CHRISTINE KATLAMA, M.D.: Okay. Sorry. No more questions. Thank you very much. [Applause]

JOHN M. MURRAY, B.S.C.(HONS), M.S.C., Ph.D.: Thank you.

JOSE R. ARRIBAS, M.D.: So the next presentation will be another raltegravir study entitled, "Rapid Onset and Durable Antiretroviral Effect of Raltegravir, a Novel HIV-I Integrase Inhibitor as Part of Combination ART in Treatment of HIV Infected Patients. These are 48-week data and will be presented by Dr. Markowitz.

MARTIN MARKOWITZ, M.D.: Thank you, and I am proud to present these data on behalf of the protocol 0014 and my colleagues at Merck. This is a truly international study done

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in seven countries on multiple continents, as well as designed and conducted with our team at Merck Research Laboratories. You have heard a lot of this this morning, but I guess I'll go over it again. Raltegravir is an HIV integrase inhibitor. It's a novel drug. It has potent in vitro activity. It is metabolized primarily via glucuronidation. It is not a sipreay [misspelled?] IV substraight therefore it does not require ritonavir boosting for dosing. In phase I studies, it was studied up to doses of 800 milligrams and was found appropriate for BID dosing, and at the 100 milligram dose had a trough level that was in excess of the predicted IC95. And because of its metabolism no dosage estimates were necessary when used with conventional ARTs.

You have heard about protocol 004. It's a two-part study with part one being monotherapy-naive patients followed by part two where combination therapy was used, and as you have heard and has been published HIV RNA decreases of 1.7 to 2.2 log were seen across the NK518 study arms and there were no differences between study arms so all doses were taken into this part two of the study. And this is part two study design. Patients who participated in part one received the same dose. Patients who received placebo received efavirenz. Approximately 150 additional patients were randomized into part two, and key inclusion criteria included susceptibility to

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efavirenz 3TC and tenofovir, no prior antiretroviral therapy, viral loads above 5,000 copies. There was stratification for RNA levels above and below 50,000, and CD4 counts needed to be above 100 cells per millimeters cubed. Endpoints included viral loads, CD4 cell counts, and assessments of adverse experiences. The hypotheses were that raltegravir in combination with tenofovir and lamivudine would be safe and well tolerated, and have comparable antiretroviral activity to efavirenz with the same backbone.

The patient characteristics were the same across groups. As you can see on this slide about 37 years or so, predominantly male, a large-percentage of non-whites, viral loads were approximately 4.8 logs, a rather healthy CD4 cell counts, and approximately a third of the patients across the arms had AIDS, a previous AIDS diagnosis at baseline. This is the disposition of all randomized patients. As you can see, the number of patients who discontinued therapy, of course, across arms was a relatively small and balanced for the efavirenz arms and the raltegravir arms. Remember, there are four raltegravir arms and one efavirenz arms. Two patients discontinued for lack of efficacy, a total of seven patients withdrew consent, and there was some discontinuations for a variety of other reasons.

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The primary endpoint was the-percent of patients with viral loads below 400 copies per mL at 24 weeks, and this is the non-complete or equal failure data. I presented the 24-week data approximately a year ago on Toronto, and you can see that at 24 weeks nearly 90 to 100-percent of the patients were below that level of protection. And the good news is that antiviral level is sustained during this subsequent 24 weeks, so when we get out to 48 weeks approximately 90-percent or so of the patients in the efavirenz arm and the raltegravir arms are below the level of detection. This is the less than 50 copy non-complete or equal failure analysis.

You have heard a very elegant analysis from John about the rapidity with which patients on raltegravir become "undetectable" or below 50 so I won't belabor that point, but at 24 weeks you can see that approximately 85 to 95-percent of the patients are below 50 copies at 24 weeks, and this effect is maintained at 48 weeks with approximately 83 to 88-percent of the patients having viral loads below detection. That's the 50-copy assay. Looking at the change from baseline in HIV RNA observed failure analysis. You can see that very potent drop in viral load in all study arms, and this antiviral activity is maintained across the 48 weeks in all raltegravir arms as well as the efavirenz-containing arm. Concomitant with the viral load responses, CD4 cell count increases were robust in all

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arms and were between approximately 125 and 200 plus cells per study arm on average.

Let me now discuss the virologic failures because I know there is a lot of interest in resistance of integrase inhibitors. In this study, virologic failure was defined as either non-response which was defined as greater than 400 copies at week 24 or early discontinuation or a virologic relapse wherein patients who went below 400 copies on their initial response they went to above 400 copies or a one-log increase above the nadir level. With these definitions, five of the patients met the criteria for virologic failure in the raltegravir group and one in the efavirenz group. Please note that patients with virologic failure were allowed to continue in the study, therefore when I told you earlier there were only two discontinuations due to lack of efficacy, so that's why there's a difference in number.

This is the genotypic analysis of patients with virologic failure. Let me first emphasize the patients on raltegravir. In the 100-milligram arm there was a patient with no response, and this patient had multiple mutations within the integrase the signature N155H along with three other integrase mutations. This patient also had changes in RT consistent with exposure to his other drugs. Please note, that in another patient with relapse there were no integrase inhibitor mutation

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seen and relapse was associated with typical signature mutations to 3TC resistance. In the patients in the 200 milligram raltegravir arm, and that's N equal 3, one of the three had the signature N155H alone, two of the patients had no changes in the integrase gene, whereas two of these patients had the signature M184V or M184I. The one patient who relapsed in the efavirenz arm had a change in the integrase that is considered a polymorphism, but had the signature G190E to efavirenz resistance and a K65R.

Adverse events were quite common across study arms, and approximately 80 to 90-percent had any clinical adverse event, but please note that the number of serious adverse events were extremely rare and balanced along study arms. Of note, drug related adverse events as defined by the following statement, investigators determined the adverse event to be possibly, probably, or definitely caused by study drug regimen, was about 50-percent in the raltegravir arms, about 70-percent in the efavirenz containing arms. Any laboratory adverse event was again relatively rare, about 25-percent. Only one patient discontinued therapy due to a laboratory adverse event, and again, laboratory abnormalities related to drug were extremely rare.

These are the common drug related adverse events seen over the 48-week period and they are relatively well balanced

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among the raltegravir group. There was a not a dose response seen as far as adverse events between raltegravir groups, and if you go down the line, I think one would predict quite naturally that the most common adverse events that were seen in the efavirenz arm were CNS related and these were relatively rare in the raltegravir-containing arms. Of note, ALT increase was seen in the raltegravir-containing arm and this was balanced in the efavirenz group as well. Serum lipids were measured during the course of the 48-week study. Total cholesterol increased by approximately 20-percent in the efavirenz arm and dropped 2.3-percent in the raltegravir arm, and this was statistically significant. LDL levels were dropped in the raltegravir arm by 7-percent and increased approximately 3-percent in the efavirenz arm. Again, this difference does reach statistical significance. And triglycerides did go up significantly in the efavirenz arm, again a statistically significant difference.

So the safety summary for this study, overall the adverse event profiles were generally similar across treatment groups. There were no dose related toxicities. Drug related adverse events were less common with raltegravir, 48-percent than efavirenz, 71-percent, and there were no drug related adverse events. Neuropsychiatric symptoms were less common with raltegravir than efavirenz, 8-percent versus 21-percent at

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week 8, 13-percent versus 29-percent at week 48. Grade III and IV laboratory abnormalities were uncommon and raltegravir had a neutral effect on serum lipids.

In conclusion, raltegravir is a promising new integrase inhibitor with rapid and durable antiretroviral effect in treatment naïve patients with viral loads less than 5,000 copies and CD4 cell counts above 100 raltegravir was active at all doses studied. It had potent activity. 83 to 88-percent of the patients were undetectable using the 50-copy assay, and the drug was generally well tolerated. Thank you for your attention. [Applause]

JOSE R. ARRIBAS, M.D.: The presentation is now open for questions from the audience. I have a question. Did these patients have baseline genotypes before they entered?

MARTIN MARKOWITZ, M.D.: Yes. The genotypes I showed were all treatment emergent.

CHRISTINE KATLAMA, M.D.: Another question Martin. So since efavirenz is once daily and ritonavir bid and if I remember correctly the study was not blinded, so what do you think could be the problem of compliance in those naïve patients? I mean could it be only those were not fully suppressed?

MARTIN MARKOWITZ, M.D.: Did you say the study was not blinded or was blinded? I am sorry. It was a blinded study.

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CHRISTINE KATLAMA, M.D.: It was.

MARTIN MARKOWITZ, M.D.: Yes. Yes, the patients basically had multiple bottles so they did not know what their assignment was, number one, so they were dosing twice daily. Adherence actually was measured in the study and the patients who did - and they had diaries - and as you know that is the most imperfect way to measure adherence. In the patients that did have virologic failure there were intermittent missed doses. But one of our patients, for example, who had wild-type at breakthrough had perfect diaries and then finally admitted to not taking drug for two weeks after three months of grilling.

CHRISTINE KATLAMA, M.D.: And you have concentration?

MARTIN MARKOWITZ, M.D.: Pardon me?

CHRISTINE KATLAMA, M.D.: Concentration, drug concentration plasma?

MARTIN MARKOWITZ, M.D.: That's not available. It's measured but not available.

JOSE R. ARRIBAS, M.D.: Question from microphone two.

FEMALE SPEAKER: [Inaudible] Brazil. What's the clinical implication of the [inaudible] viral load DK?

MARTIN MARKOWITZ, M.D.: I think this was perhaps a better question for John but I'll try to answer it what I think. I think what it looks like at this point that it's a

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combination of factors including sort of understanding that there is a mechanism whereby latently affected cells with unintegrated virus then go on to integrate and make virus, and that's a contribution to the end of the first phase and the beginning of the second phase, and that's of interest from a pathogenesis point of view and how that plays into dissemination of virus I don't think we know the answer. It does not look like that the drug gets into a sequestered site better than another drug, per se. But I think that's again the study was not designed necessarily to do very intensive viral dynamics and I think it would probably be better to do some of the studies that we have done where you hospitalize patients and get viral loads very, very frequently to really try to tease out exactly what is going on mechanistically. At this point, I think it's far too early to say whether or not there's going to be a clinical benefit per se of having raltegravir in a regimen compared to efavirenz. The 48-week data would support that the antiviral activity of both drugs is equivalent.

JOSE R. ARRIBAS, M.D.: So any idea why not even HDL increase?

MARTIN MARKOWITZ, M.D.: No. [Laughter]

CHRISTINE KATLAMA, M.D.: And one final question. I mean you take the less concentrate was defined as less than

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four, right, at six months. Some of our guidelines inferences is now more stringent for naïve patient and take less than 50 at six months. If you were going to take this analysis, did you see something arising between 50 and 400? We learned from you that everybody should be less than 50, so we have to. . .

MARTIN MARKOWITZ, M.D.: Well I think you have to remember this is a small study.

CHRISTINE KATLAMA, M.D.: Yes.

MARTIN MARKOWITZ, M.D.: Okay, so there is only 40 patients in the efavirenz arm and you are pulling raltegravir at multiple doses. The dose that has been selected for moving forward in both phase III and applying for approval is 400 milligrams. The next step is to study raltegravir in naive patients with a very stringent endpoint. Thank you.

JOSE R. ARRIBAS, M.D.: Thank you. [Applause] So now we move to NNRTI. The presentation is entitled, "The Metabolic Profile of TMC278, an Investigation on Non-Nucleoside Reverse Transcriptase Inhibitor", and will be presented by Dr. Ruxrungtham.

KIAT RUXRUNGTHAM, M.D.: Thank you very much. I feel honored to present to you the result on behalf of our multinational colleagues and coordinators the results regarding the metabolic profile of TMC278 a new generation in NNRTI. As you have heard both at Croix and also this morning with a very

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nice presentation at the plenary session by Dr. Enron about this compound, so the TMC278 is the next generation in NNRTI has been shown in vitro activity against Y-tide band NNRTI resistant isolates, and the phase I Ib which has the name TMC278 C-204 trial had 48 week results, efficacy results. And the safety profile has been shown that the potent and sustained efficacy of this compound as a once daily in a naïve population. Efavirenz is we found a little bit is a commonly associated with metabolic abnormalities, particularly increases in cholesterol and triglyceride levels.

Again, just to remind us again about the study design, so this is the design of the C204 study. Basically, the total sample size of 368 individuals had been randomized into four arms, the efavirenz arm as open-label and dose finding arm of the TMC278 is divided with 25 milligrams, 75 milligrams, and 155 milligram once daily, also combined with the selected two [inaudible], and stratified by the backbone of the NNRTI. As you can see here, about 75-percent of this study population received ATC 3TC and 25 received tenofovir FTC, and again this is a multinational study from Asia, Africa, U.S., Europe, and largely in Latin America.

And the object was to assess the metabolic profile of this compound comparison with efavirenz in this trial C204, and this is the parameters of changes from baseline has been

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analyzed. The total cholesterol, LDL cholesterol, high density lipoprotein or HDL cholesterol, triglyceride, glucose, and the assessment of insulin resistance. The samples were taken at screening baseline and various time points up until 48 weeks. So here's the demographics at baseline characteristics, and you can see that one-third of the patients were females and overall they are comparable both the median age, viral load about 75,000 copy per mL, and the CD4 approximately the median of 200 cells. This is the baseline metabolic profiles, and you can see here again, it's very comparable, look at the total cholesterol between the combined TMC278 and the efavirenz arm, LDL cholesterol, HDL, and the ratio. All these higher ratio values here are triglyceride, however there is a high variation when you look at the standard deviation of these TMC278 arm.

And this is the results of the mean changes from baseline of the metabolic profile I had mentioned at 48 weeks. The unit here is measured as milligram per deciliter. And highlights in general here, you can see that the total cholesterol, the LDL cholesterol, and HDL cholesterol in the combined TMC278 arm has significantly lower than the efavirenz arm, and you can see that the P value is below .001. And the triglyceride arm the 278 combined group also have a lower mean changes compared to the efavirenz arm with a P value below .05. Next slide. I am sorry. And to look at the plot here, this is

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in gray represent the result of the mean changes of total cholesterol from efavirenz compared to the three arms of different doses of TMC278. You can see that it is significantly different with a high P value of below .001. A similar difference can be seen with the different magnitude again, in gray efavirenz and different colors blue, red, and green from different doses of TMC278 again is very significant differences, similar findings with the HDL cholesterol level. However, when we look at the ratio of total cholesterol versus HDL cholesterol ratio there is no significant difference in the decline from the baseline of all groups. Regarding the mean changes in triglyceride over time, again there's a small increase from baseline in triglyceride from the efavirenz group but not from the three arms of the TMC278 dose groups and a P value of .05.

In conclusion, TMC278 or Epivaernz resulted in minimal changes in lipid profile at week 48, and we have potential benefit versus efavirenz. No TMC278 dose relationship in metabolic profiles. Mean changes from baseline and glucose level and insulin sensitivity were minimal and not clinically relevant for both groups. There are two parallel phase IIIs for the 96-week trial are planned and will be started by the end of this year. To end my talk, finally I would like to acknowledge all the patients participating in this study

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including the family for this cohort, all the study teams, DSMB members, Tevo Tech's coordinating staff, and all the PIs from various countries, as you can see, and for many sites in each country. Thank you very much for your attention. [Applause]

JOSE R. ARRIBAS, M.D.: So any questions from the audience? Microphone four.

MALE SPEAKER: Do you guys plan to do an DEXA scanning to measure body composition changes in both arms?

KIAT RUXRUNGTHAM, M.D.: I think that's a very good question. We will start the discussion after we see the data of efavirenz in terms of the - so I think that's a good suggestion, yes. Thank you.

MALE SPEAKER: How about any baseline differences in the amount of patients taking IV analogs in efavirenz versus 278?

KIAT RUXRUNGTHAM, M.D.: As this balance between the two arms in terms of - because 70-percent of all the participants taking ATC 3TC, yes.

MALE SPEAKER: But you did not do a baseline differentiation?

KIAT RUXRUNGTHAM, M.D.: Okay. Yes, we haven't looked at that carefully.

JOSE R. ARRIBAS, M.D.: So microphone two.

FEMALE SPEAKER: Just to respond to that question.

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KIAT RUXRUNGTHAM, M.D.: Yes, please.

FEMALE SPEAKER: There was a stratification packed into the backbone.

KIAT RUXRUNGTHAM, M.D.: Oh, I am sorry about it.

FEMALE SPEAKER: So it's adherent to [inaudible].

KIAT RUXRUNGTHAM, M.D.: Yes. Yes, so the backbone had been stratified from the beginning, and the two - I'm sorry, yes. Andrew.

ANDREW CASS: Andrew Cass, Sydney. It's a little surprising to see the various lipid fractions change less, and one reason that might be apart from the drugs is that the white changes were different between the groups. Were they the same or were they different?

KIAT RUXRUNGTHAM, M.D.: You mean the difference -

ANDREW CASS: The changes in weight in kilograms from baseline, were they the same in all the arms?

KIAT RUXRUNGTHAM, M.D.: I'm sorry. We don't have that data at the moment. Yes, that's a good suggestion to look at that, yes.

JOSE R. ARRIBAS, M.D.: Microphone two.

KATHY ANASTIS: Yes, hi, Kathy Anastis, New York City. I am wondering if you have adequate power to do subanalysis by ancestry or sex since both HDL and triglyceride vary substantially with women and people of color having better,

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more favorable profiles. In addition, having a higher increase in HDL is, of course, a favorable response so it makes it somewhat hard to determine which one actually does better in this case, which drug is actually doing better. Can you comment?

KIAT RUXRUNGTHAM, M.D.: I think we haven't looked at that subgroup analysis to look at the gender because this is a unilateral analysis. We haven't - Katir, would you have anything to add?

FEMALE SPEAKER: I just wanted to add to the previous question about weight and we did look at weight changes in these balances but there weren't any. And also for the women, there was an equal proportion of women in the efavirenz group versus the 278 groups, but yes, of course, the ratio suggestion total cholesterol subanalysis is appropriate.

JOSE R. ARRIBAS, M.D.: So I have one final question. For patients who received 278 the changes in lipids were the same if they received ATC or if they received tenofovir?

KIAT RUXRUNGTHAM, M.D.: I don't think I have that answer. Actually, it was stratified but I haven't looked at that subanalysis.

JOSE R. ARRIBAS, M.D.: Okay. Thank you. [Applause]
So now the last presentation is about the new CCR5 inhibitor is entitled, "Potent and Retroviral Activity of the Once Daily

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CCR5 Antagonist INCB (followed by many numbers) Over 14 Days of Monotherapy". It will be presented by Dr. Cohen.

CALVIN COHEN, M.D., M.S.C.: Thank you very much.

Thank you for the conference organizers and it's not so hard, 9471 is what we'll call it. So this is the first data being presented of this once daily CCR5 inhibitor 9471 given for 14 days of monotherapy. Some background on 9471 is that it is a selective CCR5 inhibitor with a 90-percent IC50 for the drug in vitro of 8 to 10 nanomolar, and when we do the correction for protein binding, the protein binding adjusted IC90, as you can see, is 50 to 60 nanomolar, and so you'll look for that target in terms of our dosage. It's also additive or synergist with other antivirals. Phase I studies were done and illustrated for us that there was rapid absorption and a prolonged plasma half-life of approximately 60 hours. There was also low peak to trough ratio, and based on some of the data that were done previous to this study, the C-trough with 200 milligrams was predicted to achieve a concentration of 400 nanomolar, and that was the dose that went into this phase I study.

Here are the baseline characteristics of a population of 23 people who participated. These were all A3 positive adults who were either treatment naïve or treatment experience. If they were treatment experienced they had no recent antiviral treatment for at least the past three months. They had a

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screening viral load of at least 4 log, and there was a 14 day dosing period with some follow-up visits as I'll show you. Mean baseline viral load, as you can see, of the population who entered was approximately 40,000 to 50,000 copies. The CD4 count at entry was over 500 as you can also see for the group, and as you can see, there were equal numbers for people who are either treatment naive or treatment exercised who are assigned to either the placebo or the 200-milligram dose.

Here are the demographics of those who enrolled. As I mentioned 23 people enrolled and all 23 completed the study, their age and their race is listed here as well as their gender. The endpoints for this trial, as you'd expect for a phase I study were the mean and median change in viral load as well as adverse events. We also have some secondary waves of viral load data that were analyzed including thresholds of the-percent who achieved various thresholds as listed here in the slide as well as the-percent below certain thresholds below 450. Here are the pharmacokinetics, and as you can see here, there are HIV negative subjects are plotted as well as those of A3 positive subjects in this study. You can see that there is similar PK in our A3 negative patient populations and A3 positive patients. As you can see here in the table, the C-max, the C-through, and the AUC are quite similar. I will also point out that we did achieve a C-trough of about 440

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nanomolar, and this again, I will remind you is about six-fold higher than what was the target for the concentration in A3 positive subjects of 394. Again, with our target of about 60 we were at least six-fold greater than the target that we were looking to achieve.

So here are the main results of the study. The antiviral activity, as you can see here, the drug was given for 14 days, and at day 14 there was a 1.7 log decline. Two days later at day 16 we achieved the nadir decline of 1.8 log. You'll notice that almost one week later at day 20, we are still 1.7 log below baseline. Indeed, at day 28 two weeks after the last dose was administered we are still .8 log below baseline. You can see here, of course, the placebo having no response at all. Shown here are the data when now broken down by patients who were either treatment naïve or previous treatment experienced. No prior CCR5 experience was allowed so this experience would include other classes, and as expected, there's no bearing of the impact of previous treatment on the activity of the drug. They are essentially superimposable whether they were treatment naive or the nine patients who are treatment experienced.

The tropism findings for this study. So tropism was determined at screening and then at baseline pre-dose, again at day 7 or day 14 and then at day 28 after dosing was

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discontinued for two weeks and then at follow up. There were two patients of the 19 who were on drug and did show a tropism change. Both of these patients had a history of treatment experienced. Patient number one was R5 at screening, as required, and also at day minus one the day the dosing was starting, but then had a dual mixed population at day 7 and again at day 28. And on some clonal sequencing data that have been done there is evidence of a dual mixed virus population that was detectable at day minus one at very low levels. Patient number two also entered with R5 screening and again at a day minus one. This patient also had dual mixed populations that arose at day 14, but then the population reverted to an R5 population at day 28. Once again, clonal sequencing would suggest that this dual mixed population arose from an unidentified ancestral virus meaning that it could not be detected, but was also different enough from the population of viruses at baseline to suggest that this was not a progression of resistance, but simply an unidentified ancestral virus that must have been mixed in the population at a very low level. Both patients, however, did revert to an R5 population after the day 28 visit in some additional follow ups, and I'll point out that these data are quite similar to other CCR5 antagonist studies that were presented as monotherapy.

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So in reviewing then the antiviral response at nadir, including now the distinction of those two patients who did have the dual mixed population as well, you can see here now breaking down the data now at various thresholds or response. We take a look specifically at the overall population or focus mainly on the population who remained R5 tropic. All patients achieved a one log or greater decline. Indeed, all but one who are R5 tropic had over 1.5 log decline, and nearly half the population achieved a two log viral load decline at the nadir. You'll notice that the nadir again, as you saw earlier, was roughly day 17 with the range shown in the details here. About 40-percent of the patients actually achieved over 400 copies but very few, of course, achieved less than 50 on this monotherapy study.

In terms of the safety of the drug there were no serious adverse events noted and no discontinuations for any reason. If we take a look at the adverse events that were reported they were all of mild severity. There were four people who had at least one adverse event. Those adverse events are listed here. They were GI or other in origin. One person had three adverse events. The others were had by one patient only. Additional safety results, there has been a focus on the QTC issue based on data from either some annual work as well as other CCR5 inhibitors and so that was done

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here. In terms of looking at the QTC prolongation there are two ways this was measured. One is to take a look at the mean change from baseline with a prolongation from baseline considered a worrisome finding, but here in this case there was, in fact, a shortening, no prolongation was observed for the mean change for those on drug, and in fact, very similar to placebo.

The other way this is analyzed is to take a look at the-percent of subjects who have a prolongation by over 60 milliseconds and no patient had that on placebo or 9471. Using a more conservative approach of looking at 30 milliseconds, a range that is an answer in clinical significance, you'll see that that was one patient on placebo and three on 9471. In terms of transaminases, you can see that there were very few people who had grade I increases and these were typically transient and resolved either during dosing or after. No patient had grade II or greater, and there were no other changes observed with chemistry or hematology parameters that were measured for the time period of the study.

So finally, in conclusion 200 milligrams of 9471 for 14 days was well tolerated. We observed no clinically significant chemistry, hematology, EKG events, none of these were observed. There was a rapid biologic response with a mean maximal viral load decline of 1.8 log observed at day 16. 16 of the 19

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participants had a viral load decline of at least 1.5 log, and 16 of the 17 who remained R5 tropic had a 1.5 log or greater decline. You will, of course, note that the viral load did stay suppressed beyond the dosing interval, and in fact, that is consistent with the prolonged plasma half-life. And again, I will remind you that at day 28, two weeks past the last dose, the viral load was still .8 log below baseline. Two patients had an unmasking of an X4 using virus population, and as I mentioned, on preliminary analysis these X4 populations appear to be arising from preexisting variance. And therefore, we have concluded that 200 milligrams once daily warrants longer term phase IIb studies in R5 screened population. The safety and activity of other once daily doses of 9471 are currently under investigation and phase IIb studies are planned for one or more of these doses. So I would like to acknowledge my co-investigators who participated and the patients at these sites, the folks at Monogram for their work on the profile assay, the group at Insight who have been helping us develop this compound, and of course, I3 Research. Thank you for your attention. [Applause]

JOSE R. ARRIBAS, M.D.: Questions? So Calvin, is this direct C3A4 substrate or inducer?

CALVIN COHEN, M.D., M.S.C.: Yes, thank you very much. So this drug is neither an inducer or an inhibitor of 3A4. The

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drug, however, is a substraight for the 3A4 system and so now work is now going on with other doses in the presence of ritonavir to explore how we will have to alter the dose in the presence of ritonavir and that work is now ongoing in the next phase I studies.

CHRISTINE KATLAMA, M.D.: You mentioned that the patient has at trough test screening at baseline and this type II test which exhibit R5 some were not detected as dual mixed. [Inaudible] I mean it's not specifically to this drug, but what is your comment about that? How often will we have to follow with these tropic tests and what can be the confidence rate in the test?

CALVIN COHEN, M.D., M.S.C.: Thank you very much for that questions. That's very kind, and I appreciate that. So can I have my next slide, please? [Laughter] So, I guess -

FEMALE SPEAKER: You like the difficult questions.

CALVIN COHEN, M.D., M.S.C.: Yes, thank you. I knew I could count on you. So I guess what I could say, Christine, is the field is trying to I think grapple with exactly the point you raise and perhaps an improvement in the sensitivity of the assay or other assays will be necessary for us to increase the confidence that we know the patient population that we are treating. But I think analogous to the issues in resistance in which minority variance do show up as potentially relevant even

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in conventional resistance assays I think we have this challenge in all of our drug classes. I don't think the challenge is limited to R5, though I appreciate that that is a problem being observed in this class, but non-nucleoside resistance seems to emerge even when conventional assays say there is a wild-type virus. So I think that this is a challenge for our field in a boarder way.

JOSE R. ARRIBAS, M.D.: So microphone four.

OWEN COPLEY: Hello. Owen Copley from Monogram Biosciences. Cal, I want to relieve you a little bit there.

CALVIN COHEN, M.D., M.S.C.: I thank you, Owen.

OWEN COPLEY: In the experienced population from the data that we have for those repeated testing done, the switch rate between screen and baseline is between 8 and 10-percent, and that's based on the available data. That looks like that represents cloning actually biological circulating virus in the region of a few-percent, 2 to 3-percent, and I think there is a growing sense that that actually is clinically relevant to this class. In naïve individuals when we look at screen to baseline it's actually about 3-percent, so it's much less frequent representing, I think, the actual underlying biology. And with regard to your comment on sensitivity, actually we have a very active program looking at enhancing sensitivity down to levels around 1-percent or less.

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CALVIN COHEN, M.D., M.S.C.: Excellent.

OWEN COPLEY: Thank you.

JOSE R. ARRIBAS, M.D.: Cal, can this drug be given less frequently than once a day?

CALVIN COHEN, M.D., M.S.C.: Well certainly the plasma half-life would suggest that it could, and indeed, in the presence of ritonavir which appears to prolong the half-life, that's one of the questions that we might be exploring in the future. Thank you very much.

JOSE R. ARRIBAS, M.D.: No more questions? [Applause]
So with that I would like to thank all the speakers for the excellent presentations and now the session is closed. Thank you.

[END RECORDING]