



Transcript provided by kaisernetwork.org, a free service of the Kaiser Family Foundation¹
(Tip: Click on the binocular icon to search this document)

**4th IAS Conference on
HIV Pathogenesis, Treatment and Prevention
Late Breaker Track B: Clinical Treatment and Care Track
Session 2
International AIDS Society and
Australasian Society for HIV Medicine
July 25, 2007**

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

[START RECORDING]

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: On behalf of [inaudible] I'm Janet Darbyshire from the Medical Research Council in the U.K. Clinical Trials Unit and for my co-chair Dr. Hector Perez from Buenos Aires. Our first speaker this afternoon is Dr. Bill Olsen from Progenics Pharmaceuticals in Tarrytown, U.S. who is going to present on the Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV-Infected Individuals. Dr. Olson.

W.C. OLSON, PH.D.: Thank you very much for the introduction and thanks for the organizers for the opportunity to present and thanks to the audience members for participating this late in the conference.

We are very excited to be here today and describe the proof of concept study of our CCR5 Monoclonal Antibody PRO 140. This study was designated 1302 and was the first to test for 140 in HIV infected individuals. The study benefited from a distinguished roster of investigators as listed here including Mike Sag, Jeff Jacobson, Melanie Thompson, Margaret Fishel and the others indicated on the list here. I also wanted to note our thoughts today are with our dear friend and colleague Joe Stovola. Joe was the medical director for this protocol at Progenics and Joe was recently killed in tragic automobile

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

accident and today's presentation is given in honor of Joseph Stovola.

I'd like to continue with an introduction to PRO 140. PRO 140 is our humanized CCR5 monoclonal antibody. It varied broadly and potently inhibits CCR5 mediated HIV entry in vitro. I could spend the entire session describing how PRO 140 is different from small molecule CCR5 antagonist. Such that, these two in many respects, represent distinct classes of CCR5 inhibitors. Perhaps for the purposes of today, suffice to say that there fundamental differences in the way in which PRO 140 and small molecule CCR5 antagonist recognize CCR5 and inhibit R5 HIV. In many respects these differences are very similar to the differences that one sees for nucleoside analog reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. A similar case where they both recognize RT in a very different manner and inhibit HIV in a very different manner.

To the manner at hand, the 1302 study was in a sense a classic monotherapy study. This was a randomized, double-blind, placebo controlled study designed to evaluate the tolerability antiviral activity and pharmacokinetics of a single intravenous infusion of PRO 140 in HIV infected individuals. These were individuals with easily measurable levels of virus that required CCR5 for entry. They had

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

relatively high levels of CD4, no AIDS defining illness and no antiretroviral therapy for at least three months consistent with the early stage nature of the disease. A total 39 subjects were treated with placebo or PRO 140 at the indicated dose levels. They received a single intravenous infusion and then were followed for 59 days. Individuals were followed for safety and efficacy and pharmacokinetics and pharmacodynamic effects of PRO 140. Today we'll have the opportunity to discuss antiviral effects and safety, but not PK/PD relationships. There only so much you can fit in 10 minutes and plus we're going to present the PK/PD information at the upcoming ICAC Conference. That will be an oral presentation by our longtime colleague Jeff Jacobson and I would be remiss to upstaging Jeff's presentation by discussing PK/PD today. Just stay tuned for that information please.

So this slide illustrates the baseline characteristics of the subjects. There are nice placebo subjects in 10 in each of the PRO 140 treatment groups. Each individual received a single intravenous infusion and each individual completed the 59 day followup period. In general, the study was reasonably well-balanced for a small study of this size. The median HIV RNA of entry was 27,000 copies per mil, CD4 cells averaged about 480 cells and we were encouraged by the participation of women and minorities in this study.

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

This slide illustrates the antiviral effects. Here we have plotted the mean locked and change in HIV RNA as a function of time following a single intravenous infusion of placebo or PRO 140 at the indicated dose levels. So the antiviral effects were potent, prolonged and dose dependent. [Inaudible] PRO 140 reduced viral loads on average by 1.7 log or 98-percent at day 10 with individual reductions ranging to 2.5 log. To our knowledge, these are the largest viral load reductions reported for just one dose of any HIV agent. Viral load reductions of about one log were observed at day 5 and then continued for two to three weeks post dosing. As you might imagine, the results were highly significant for both the 2 and the 5 in the mg per kg dose groups.

So there are many ways to interrogate the data. Here we have the mean locked and change in HIV RNA for the different treatment groups. The blue bars represent the day 10 results from the prior slide. Of course not every subject had a viral negative at day 10; in some cases it was day 12 or day 15. That's captured in the green bars. Here we have the average of the individual nadirs [misspelled?] regardless of study date. In this case, the 5 Mg per kg dose group had a 1.83 log₁₀ reduction. And again we have a high degree of statistical significance for the 2 and 5 mg per kg dose groups. We also considered the percentage of subjects who responded with a

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

greater than ten-fold reduction in HIV/RNA and that's illustrated here. Once again we see a nice dose response relationship with a 100-percent dose rate at the top dose group.

This slide illustrates the results of co-receptors tropism and testing as performed at Monogram Biosciences. Just over 100 subjects were screened for this study. Of those, 81 had R5 only virus. That's about the right ratio for the study population. Of those, 42 were excluded for other reasons and 39 were treated; 30 with PRO 140, 9 with placebo. While on study a dual mixed tropism amass result was observed in 1 of 9 placebo subjects, and 1 of 30 PRO 140 subjects. The PRO 140 subject was in the low dose group and the dual mixed tropism result was observed in a single day only. All other days, including study discharge, the tropism result was R5 only.

Now I think that we as a field are just beginning how to interpret data like these. But it is noteworthy that the incidents of dual mixed tropism as a result was observed no more frequently in the PRO 140 groups than in the placebo group. Now we have initiated studies to determine, of course, whether dual mixed viruses could be detected at baseline in these individuals.

So in terms of safety, the study was relatively uneventful in terms of safety. The most commonly reported

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

adverse events were headache and nausea and they were reported with similar frequencies in the placebo and PRO 140 groups. Apart from that discussion of safety is really a discussion of what we didn't see. There were no drug related serious adverse events, no dose limiting toxicity, no obvious pattern of toxicity and no signals of the type that have been reported for small molecule CCR5 antagonists such as QTC issues, pattern toxicity or postural hypertension. In addition, there was no change in plasma levels of the CC chema kilates. There was, however, a trend towards increased CD4 cells in the high dose group. This manifest itself as 129 cell increase or 29-percent increase at day 8. And these levels persisted at three weeks post dosing. Of course, potent antiviral suppression often leads to a redistribution of CD4 cells, and that could be the case here. I think regardless of mechanism, we are encouraged by the fact that the trend is in the right direction.

Just to summarize the main findings of this study. In terms of antiviral effects, we believe this study demonstrated that PRO 140 is a potent antiretroviral agent with prolonged single dose activity and we were encouraged by the fact that these potent antiviral effects were observed at well tolerated doses of study drug.

Next steps for PRO 140 include completing the PK/PD analyses in time for presentation at ICAC. We have the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

opportunity, if we wish, to meet with FDA to discuss these findings prior to initiating additional clinical studies. And these studies could include the intravenous formulation, as well as new subcutaneous formulation. And I'd just like to spend a minute or two on that. We believe the feasibility of subcutaneous of PRO 140 is supported by the potent and prolonged antiviral activity that we just say, as well as the favorable solubility of PRO 140 at neutral Ph in user friendly buffers, as well as outcomes in recent six month animal safety studies and bio availability that PRO 140 demonstrated in those studies. Putting this all together would suggest, at least, that weekly or even every other week dosing of PRO 140 would be predicted to provide antiviral drug levels. And that's exciting to us that because means potentially subcutaneous PRO 140 would able to provide potentially the first long-acting, self administered therapy for HIV. This will be a situation, at least for this drug, treatment is not every day, once-a-day, three times a day, it's once a week or every other week. And again self administered by the patient.

This slide illustrates how we view PRO 140. Really for us the paradigm is not so much fusion, but more other subcutaneously administered monoclonal antibodies. And here I have just listed the approved uses of the approved drugs along with a target profile for our investigational agent. So we

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

like fusion, sub-q PRO 140 would be used subcutaneously on a chronic basis for the treatment of HIV infection. But that's where we believe the similarities end and the differences become important. In terms of molecular class, frequency of administration, user friendliness of the buffer, and injection site reactions we believe that PRO 140 stands to be quite different from fusion and more akin to sub-q monoclonal antibodies. And I see the red light is beeping at me so I'll just finish very quickly by thanking a small fraction of the many, many contributors to this program. That includes obviously the subjects of the 1302 study team and this is the very small list of the many contributors at Progenics. We thank our colleagues at Monogram Biosciences and we're very grateful to the National Institute of Allergy and Infectious Diseases for the continued support of PRO 140, NIAD and the Division of AIDS has supported PRO 140 at every stage of its development. With that I'll stop and thank you for your attention. Thank you. [Applause]

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: Thank you very much Dr. Olson. I think we've got time for a few questions. So please, anyone who would like to ask a question tell us you are, where you come from and please be brief so we can have as many questions as we can. I see someone at microphone two.

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

PIETRO BANASTRA: My name is Pietro Banastra from Switzerland. I'd just wondered, given the restriction to R5 whether you have thought about developing the drug as a pre-exposure prophylaxis, which would make much more sense to me.

W.C. OLSEN, PH.D.: There's been some discussion along those lines and we are working with one group along these lines. We're working with a group in San Diego to do this. It's not the main thrust of our program, but we recognize the potential of that drug in that setting. Thank you for that question.

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: I think someone's rushing up to microphone two quickly.

ABRAHAM HEVE: Abraham Heve from John Hopkins International. I have a question. It has to do with the use of monoclonal antibodies. Generally speaking, they are associated with PBME. So what do you think of using it in those sub global patients and probably the incidents of TB in those patients.

W.C. OLSEN, PH.D.: I'm sorry, the incidence of?

ABRAHAM HEVE: TB.

W.C. OLSON, PH.D.: Oh, tuberculosis. Well, I think a monoclonal antibody without drug-to-drug interactions, without any expectation that the drug would have significant drug-to-

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

drug interactions; it potentially could be a good application for a drug like this. Thank you for that question.

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: There's a question at microphone one.

MICHAEL LETTERMAN: Yes, Michael Letterman, Case Western. Could you tell us a little more of the interaction of this antibody with the receptor, whether it blocks ligand receptor interactions or agonizes?

W.C. OLSON, PH.D.: Thank you for that question. That's my favorite question. So PRO 140. We have mapped the epitope for PRO 140 to elements within the amino terminal domain and the second extra cellular loop. At least in vitro models there is this window between inhibition of HIV infection and blocking the natural activity of CCR5. It's about 100-fold difference between concentrations required to block the natural activity and the concentration required to inhibit HIV. And we'll see whether that offers some kind of advantage in man. Thank you.

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: Okay, thanks very much indeed. I think as we've got really a tight timetable today to ready to have the racketeers following on, we'll thank Dr. Olson very much for his presentation and move onto our second presentation which is to be from Dr. Tim Jenkins, a clinician at Pfizer Global R&D, of some which in the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

U.K., whose going to talk to about the Short-Term Monotherapy With UK-453,061, A Novel NNRTI, which Reduces Viral Load In HIV Infected Patients. Dr. Jenkins.

TIM JENKINS, PH.D.: Thank you. It's a pleasure today to present to you the results from our study A5271010. By way of introduction I should say that UK-453,061 is novel nucleoside reverse transcriptase inhibitor for the treatment of HIV.

In preclinical studies, UK-453 is shown to be active against wild type virus and from primary islets and also UK-453 displays balanced activity against drug resistant NNRTI mutations. In vitro experiments designed to develop resistance against UK-453 have shown that two to three mutations are required to obtain resistant virus and these virus which are now resistant to UK-453 are still sensitive to efavirenz [misspelled?]. The combination doesn't appear to inhibit efavirenz, has a large set of toxicity index and is predicted to have good CNS penetration.

As shown in the post earlier today, UK-453 is shown to be safe amongst R rate single doses up to 1.8 grams and multiple doses of 2 grams a day, that's given as 1 gram b.i.d.

The most frequent adverse events seen from the multi-dose studies have been diarrhea, abnormal bowel sounds, abdominal discomfort, flatulence, dyspepsia, and headache. And

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

in either the single dose studies or multiple dose escalation studies a maximum tolerated dose has not been identified. No significant trends in lab safety parameters were observed and UK-453 appeared to have predictable PK and there is no significant in UK-453 plasma AUC in the presence of a high fatty meal.

Well, coming onto the study A571010. The objectives were to examine the effects of seven day monotherapy on viral load to see to understand the PK/PD relationships and also the safety and tolerability of UK-453. The patient population was HIV infected men with no prior exposure to NNRTI and the absence of any virus that contained NNRTI resistance mutations, a CD4 counts about 250, a viral load above 5,000. They could be treatment naive or could be treatment experienced, but they need to be off treatment for at least eight weeks prior to screening and obviously they need to be diagnosed at least three months prior to screening.

The design of the study was that it took place as a randomized, double-blind, out patient study, and it took place in two stages. We used modeling in simulation work to establish the correct doses to choose and also minimize patient numbers. There were six patients per arm and patients were dosed for 7 days. There was a PK done on day 8 and patients then followed up until day 40. Viral load measurements were

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

taken at screening randomization and day 1 prior to dosing and then for the days indicated on the slide. The first stage using suspension had doses of 10 mg b.i.d., 30 mg b.i.d., 100 mg b.i.d. and 500 mg q.d. and the second stage using tablets had doses of 100 mg q.d., 750 mg q.d., and 500 mg b.i.d. A total of 81 patients were screened. We had 49 randomized ones subjected before our first dose and so was replaced, so we had 48 patients complete the study. And as you can see here, we've got the baseline characteristics of the subjects.

This is the first result figure for UK-453 and it's looking at the median plasma concentration of 453 versus time for day 8. UK-453 PK in patients appears predictable and the plasma concentrations in UK-453 in this patient study appear to be similar to levels seen in healthy volunteer studies. Here are the log₁₀ viral load changes from baseline to day 8 and also to by dose with highest b.i.d. and q.d. doses highlighted. Doses equal to a greater than 500 mg total daily doses resulted in similar viral load reductions for a mean decrease from baseline of equal to or greater than 1.7 log reduction and although it's not shown on the slide here, all patients dosed 500 mg daily dose or greater achieved equal to or greater than 1.5 log reduction at nadir [misspelled?].

Here's the plot of the mean reduction viral load at the dose against time and most dose appear to reach nadir after the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

last day of dosing. And again showing the doses above or equal to 500 mg total daily dose appear to be similar viral reductions.

As mentioned, patients were excluded if they had prior exposure to either an experimental or a marketed NNRTI or the presence of virus that contained NNRTI mutations and during the screening of the patients, seven out of the 81 patients screened were excluded for the presence of NNRTI mutations. All patients who were included in the study had further genetic analysis on day 1 prior to dose, day 8 after dosing, and then followup on day 40. There was one patient on 100 mg q.d. was observed to have a mixture of Y1801Y, Y1801C, on day 8 only. And there two patients on 750 mg q.d. who were found to have Y144F on day 8 only. Now Y144F is not previously been associated with resistance to UK-453, and therefore we are examining this mutation in vitro to see if it has any effect on any UK-453 activity. I should also say we have a number of crystallographic [misspelled?] structures of HIV/RT with UK-453 bound and in fact they'll be presented next month at the European Crystallography meeting. Looking at these structures, UK-453 are bound to reverse transcriptase, Y144F appears to be located well away from the binding to the compound. There are no other known NNRTI or UK-453 resistant mutations as seen in any other group. Also, we're currently undergoing the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

subsequent monoclonal deep sequencing analysis. The results will probably be presented, I guess, at ICAC.

UK-453 appears safe and well-tolerated in this patient population. There was one treatment related serious adverse event. That was hospitalization on day 14 and two non treatment related severe event due to food poisoning for one individual on day 2. There were no discontinuations due to [inaudible] or lack of toleration. As you can see, the most common oral causality ASE [misspelled?] for three or more patients was real mild and moderate were cold, flatulence, headache, fatigue and nausea.

And here's a table of the all causality and emergent ASE occurring in more than one subject in any one treatment group. The ASE was mild-to-moderate and these ASE were similar to what we have seen and observed in healthy volunteers.

So in conclusion UK-453 appears to be generally safe and well tolerated at all doses evaluated in this study of HIV infected men. Doses of 500 mg b.i.d. or 750 mg q.d. achieved a mean decrease baseline HIV nadir values of 1.9 and 2 log respectively. And that for further evaluation of q.d. and b.i.d. doses of UK-453 doses of the treatment of HIV is merited.

And finally, acknowledgments and thanks. We'd like to thank all the patients who were willing to participate in this

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

study, the investigators and staff who worked so hard into the sites in Cologne, Frankfurt, and Hamburg. And finally thanks to Pfizer colleagues in Germany and Pfizer colleagues in [inaudible] who discovered UK-453 and to be working on its development. Thank you very much for listening. [Applause]

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: Thank you very much Dr. Jenkins. You left us plenty of time for questions. Please again, tell us who you are, where you're from. Do we have any questions? Microphone one. And microphone one is lit up, I don't see anyone. No. Microphone two, there's a person on the microphone.

MALE SPEAKER 1: Can we assume that you seem to have very effective viable liquid formulation that children are going to included in your clinical program?

TIM JENKINS, PH.D.: Well, I guess the development of this compound is still very early, but I imagine once we understand that this compound is safe in long-term therapy then those things will be under consideration.

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: And the second question from microphone two.

MALE SPEAKER 2: I'm [inaudible] from Hamburg, Germany. What was the reason only to include men? Are there any [inaudible] studies in animals, and any problem with the drug in females?

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

TIM JENKINS, PH.D.: Again, this is a very early stage in development we have actually in some of the studies I'm not showing here in phase 1 studies included women. For this study, we didn't have all the results from the toxicology stages and some of them are strong bearing as well.

JANET DARBYSHIRE, O.B.E., M.D., F.R.C.P.: Okay, if there are no more questions, thank you again to Dr. Jenkins and I'd like to hand over to my co-chair [applause] Dr. Hector Perez having given you plenty of extra time.

HECTOR PEREZ, M.D.: Thank you Janet. The next speaker is Dr. Pedro Cahn. Dr. Pedro Cahn comes from Western Nation Buenos Aires, Argentina. The next paper is Superior Activity of Apricitabine Compared to 3TC Over 21 Days in Treatment Experienced HIV-1 Infected Patients Failing Therapy With M184V and NRTI Resistance.

PEDRO CAHN, M.D., PH.D.: Thank you very much for giving me the opportunity to present this data on behalf of my co-workers in Argentina and also in Australia.

ADC or Ardecitoline [misspelled?] is a [inaudible] analog. Its proof straightforward is reported in [inaudible] by gene determination. It has been shown in former studies to be at different HIV strains including islets currently at one interval [inaudible] and one other nucleosides [inaudible] mutations. It has shown very low toxicity including very low

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

microconidial [misspelled?] toxicity and it doesn't any metabolic problems, no evident interactions with other drugs. The drug is to be administered orally with or without food. This is phase 2 randomized, double-blind study dose ranging comparing 3TC one arm and two different doses of 3TC. In treatment these patients are suspended for conditions for any was to carry the M184V mutation. Patients had to be priorly [misspelled?] exposed to at least two different classes of antivirals, they had be failing at 3TC regimen, they also could be failing FTC that way we didn't have any patients on FTC in the trial. Also, they had to show at least 2,000 copious in viral load and any number of times were allowed. We had two primary inputs. One was the mean time without change from baseline in viral loads at 21 days and the second was the absolute change from baseline on day 21 again.

So here you can see the study at this time failing patients occurring the M184V were in the blinded manner assigned to either 3TC at the standard dose or at the 600 mg b.i.d. or 800 b.i.d. and they were exposed to functional monotherapy with these drugs until day 21, when on the basis of treatment history and genotype they were optimized. And continued on study on their current arm until week 24, at which point in time, all patients will be switched to open label Apricitabine. If the patient would have failed to get at least

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

half a log drop in the viral load by week 12, the patient would be offered to return to an open label followup.

Here you can see the demographics. Most of the patients were included in Argentina. We had about 70-percent and 30-percent female and the majority had viral load below 100,000 copies. The number of times, as you can see, almost half of the population had less than three times and the other half, obviously, three or more.

As you can see here, this is the time of change in viral load. Viral load was censored at day 7, 14 and 21. And as you can see, as expected through this here showed almost no change and both arms showed viral load reduction starting on day 7, and the absolute change is seen in this table in which I draw your attention to the upper line in which you can see, as expected there is no change noted in CBC and the viral load is 0.9 log in the 600 mg dose and is 0.721 log in the 800 mg dose. This was not a preplanned analysis but we decided to look at those patients who had more than three times at baseline. As you can see here, again no significant changes in the 3TC arm. In the 600 mg arms, the performer was 0.37 but 800 mg arm you can see it was a nice reduction of points in the five logs.

What about the genotypes? We are reminded that this is a function of monotherapy with a nuke [misspelled?], so you wouldn't expect to find a lot of patients unaffected. Even so

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

we could only genotype 38 patients out of the 51 patients, and as you can see, all 38 patients maintained the M184V mutation during the observation period. Four patients lost one time, which I think was just a matter of detection. One patient in the 3TC arm and three in the ATC arm. Four doses were gained one time at day 21, they were all on ATZ, two in the three arm, and three in ATC arms. No patient gained K65R, 74WE or any other mucocyte mutation during the observation period.

The drug looks pretty clean in terms of safety, as you can see no serious adverse event - no patient had to discontinue due to adverse events. All adverse events were almost mild or moderate and only we could identify as per - assess per the investigators one drug related adverse event in the 3TC arm, peripheral neuropathy exacerbation, one case of nausea in the 600-milligram, one case of mild dyspepsia and anorexia - two cases, I'm sorry, in the 800-milligram arm. Regarding the severe adverse events, none of them seem to be related to study drug - one in the 3TC arm - hyper [inaudible] and one in the 800-milligram ATC arm, a case of thrombocytopenia that was previously established before the patient was exposed to the drug and showed up again during the study. So in conclusion, [inaudible] demonstrated superiority [inaudible] activity in patients with N184B plus/minus [inaudible] with a nice viral load reaction of 7.2 to .9 log

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

[PH] over 21 days of function on monotherapy and even in patients with more than three times .75 was achieved. No evidence of resistant development after 21 days of functional monotherapy. The N184B mutation was maintained in all patients with a [inaudible] virus and we were unable to identify any new nucleoside [misspelled?] analog mutations. The molarity of both doses was excellent and similar to 3TC and I can say it's maintained to date because the study's ongoing and we expect to present the 24-weeks result early next year. I want to acknowledge all the patients and researchers participating in the study. Thank you for your attention. [Applause]

HECTOR PEREZ, M.D.: Thank you Pedro. The paper's open to questions. [Inaudible].

TOM GAMBLE: Tom Gamble from Colorado. Has this drug been studied in patients who are wild type at position 184 and if so what is the antiviral activity with wild type 184?

PEDRO CAHN, MD, PHD: Yes, we performed the study but that was presented two years ago and with the 600- and 800-milligram dose, we got about 1.6 logs viral load reduction in a 10-day monotherapy study.

HECTOR PEREZ, M.D.: More questions? No? Thanks Pedro. Okay [applause] the next presentation is Dr. Christine Katlama from Pitie-Salpetriere Hospital [inaudible], France. She will be presenting Duet 1 and 2, 24 weeks, results of the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

phase III randomized, double-blind trial to evaluate efficacy and safety of TMC125 versus placebo in treatment-experienced HIV-1 infected patients. Thanks.

CHRISTINE KATLAMA, M.D.: Thank you. Good afternoon everybody and I would like to thank the organizer not only for selecting our abstract but also for asking to put two abstracts on one and also for being the last presenter of this session. I would really thank Anthony Mills who have very [inaudible] and gallantly lead this non-English speaking woman from Europe. So you can see this [inaudible] graph here of Duet 1 and Duet 2 - don't ask me the logic because you have France in Duet 1 but you have Europe and you had two [misspelled?] Europe a mix in Northern and Southern studies too. So Duet 1 and Duet 2 are two large, 600 patients per trial, one of my studies evaluating TMC125 - 200-milligram BID versus placebo on the top of the background containing darunavir - booster darunavir regimen with an optional [inaudible]. The primary end point analysis is at 24 weeks and these are the data I am going to present to you. The overall study period is 48 weeks with an optional 48-week extension you might see one day. To be eligible, the patient had to have a viral load greater than 5,000 copies [misspelled?] and a stable [inaudible] for eight months. They have to be resistant to NNNTI [misspelled?] with at least one mutation at screening or in documented history [inaudible] and

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

also they have to have at least three primary PI [misspelled?] mutations at screening and again a very - it was new - I mean the primary end point new for this design experienced patient. The primary end point of note with the proper [inaudible] achieving a viral load less than 50 copies [misspelled?] at week 44 - at 24. So here is a baseline characteristic of the patients. The majority of them were Caucasian men. The median viral load was approximately 4.8 log [misspelled?]. The median CD4 was around 100 cells [inaudible]. The patients were highly experienced. Two-thirds of them had received a prior ten to fifteen antiviral drug. Five percent of them are being exposed to decemvir. They were also harboring highly resistant virus with 60% of them having greater than 200 NNTI [misspelled?] resistance associated mutations and again, 2/3 having more than four primary mutations. Enfuvirtide [misspelled?] was used by 40% of the patients but only de novo use in 25% of them. Despite optimization of NNTI [misspelled?], despite the use of darunavir, and the option to use Enfuvirtide, 15 to 18% of the patients had no active drugs in the background with a PSSA equal [inaudible] and but further - 30% had only one active antiviral drug. So now looking to the primary end point, which is the viral load undetectable less than 50 copies at week 24. You see that in these experienced patients with very few treatment options, TMC125 plus the background of booster

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

darunavir results in high resistance rate with approximately 60% less [inaudible] to Duet 1. Where you can see in [inaudible] that TMC125 - there was a 56% of the patients with which viral load below 50 whereas it was 39% in the placebo group. A very similar result seen in Duet 2 with 62% of undetectable [inaudible] below 50 copies compared to 44%. The high proportion of responders in the placebo group is due probably to the almost universal use of darunavir de novo and in fact, the virological response is achieved here is very comparable to what has been regarded with darunavir in the power studies. Now if we look to our slightly less stringent criteria of less than 400 copies, you can see that the results are even much better with 74% of the patients below detection compared to 51% in Duet 1 and 75% again below 400 copies compared to 54 in Duet 2. These differences are also highly significant. Now if we look to the viral reduction in those two trials from baseline to week 24, you can see that a very nice reduction is achieved with less than - -2.4 logs in the TMC125 group in Duet 1 compared to 1.7 in the placebo group. These are very similar in Duet 2 with a 2.3 log reduction in the TMC125 group compared to 1.7 in the placebo group. Now if we look to the change in CD4 second from baseline, again in Duet 2, there is an increase of +89 CD4 compared to 64 in the placebo group. The difference is statistically significant and

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

please know that this represents from baseline an 80% increase, which means clinically a lot in those patients who are around 100 CD4. In Duet 2 there was also a greater increase in CD4 in the TMC125 group with +98 compared to 66 in the placebo group but here are the results did not reach statistical significance. The reason why the reason there is a difference in the two studies isn't clear but we might also think that the recovery of CD4 is slow in some patients and with an extended follow up, there might be a difference. So now moving on to looking at the response of TMC125 again, below 50 copies according to the number of the active background drug. You can see that. In case of no active drugs - I cannot see this here - in case of very few active drugs here - I'm sorry - it's here that there is the best advantage of TMC125 with 47% reaching undetectability below 50 copies compared to 9% in the placebo group. The differences were also very high in the case of having only one drug. As soon as you have two or three or more drugs, TMC125 performed better but the difference was less. This really suggests that once you have two free active drugs probably a third one is adding little benefit and very similar results are seen in Duet 2 before - again. Forty-four percent of the patients with no active background reached undetectability compared to 7% in the placebo group and you can see all of the [inaudible] and very similar results. Now the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

primary analysis of these trials divided the patients according to the [inaudible] and again I'm sorry, this is slightly complicated but not that much, you have on the left side the patient who either reused Enfuvirtide or [inaudible] not using Enfuvirtide and on the right side, the ones who are using Enfuvirtide and as you can see here, there is much higher benefit in those who are reusing or not using Enfuvirtide of TMC125 with 55% of the patients reaching below 50 copies compared to only 33% in the placebo group. Slightly in contrast, in those who use on top of TMC, darunavir, Enfuvirtide de novo, the difference with the placebo group was less pronounced and you have exactly similar results in Duet 2 with rather this very nice activity. So now what is the [inaudible] response according to baseline mutation? Thirteen - baseline resistance mutations have been associated with decreased response to TMC125 but will be called TMC125 RA [misspelled?] and you can see the list - 906 [misspelled?]. Importantly you can see that there is not the K103N but even as clinical person we know which is very fickle in our NNTI resistance patients. So now when we look to the response, the virologic response according to the number of mutations, you can see that in the absence of any of these 13 mutations but which may include any other NNTI mutations, you have a nearly 80% of antiviral response. One mutation, 61 and 2 mutations,

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

60. It's only after 3 and more mutations that there is decreased response to TMC125 but of note and very importantly in all these big number of patients, it was only 14% of these who had three or more TMC125. So this situation is very infrequent in the clinics. So now we wanted to see the effect of one particular mutation, the Y181C on TMC125 response. So this is a very common mutation, which confers a high level of resistance to currently available NNTI and if you can see here, the blue bar represents the other response to TMC125 and this bar here show you that when there is the Y181C a lot, there is still a 60% of virological response. When the 181 - this mutation is [inaudible], nearly 60 and it's only when there is three or four mutations in addition to the Y181C that there is a decrease efficacy but again this is a very infrequent situation in the clinics which concerned in this particular trials only 13% of the people. Overall, there are [inaudible] in the TMC group were very similar to the placebo. I have just outlined the most important data. You can see the discontinuation due to adverse events were very [inaudible] around 5% that was rash and I will come back to that and importantly the nervous system disorder or psychologic disorder were seen with a similar frequency or even lower in the TMC125 group compared to the placebo and this is very notable. This type of adverse events are known to be associated with the use

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

of an NNTI. So back to the rash, the overall incidence was 17% in the TMC125 group and 9% in the placebo group. It's most frequently as usual in the second week of therapy, this was very mild, usually mild to moderate with 1% grade III and 0% grade IV, very important thing was there as no [inaudible], no severe things and these led to a very infrequent discontinuation of the treatment mostly self-limiting despite continuation of treatment. There was a higher incidence of rash in women but there was no association with an increased severity, no treatment discontinuation. Neither was association between the rash and baseline CD4 count and again, very important in the clinics, in patients with a history of an NNTI related rash, there was no apparent increase. So now moving to the incidence of grade III or IV laboratory abnormalities including the lipids and the liver parameters, there was generally similar between TMC125 and placebo and really no other clinical relevant abnormalities. So in conclusion, from these very large, double-blind, randomized, controlled trials, DUET 1 and 2, we've seen the TMC125 consistently demonstrates the priority of a placebo in those treatment experienced patients including those with an NNTI resistant virus with 56% of Duet 1 patients and 62 in Duet 2 of the patients achieving a viral load suppression less than 50 in the context of a background that includes darunavir. Even the

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

absence of any other free active background regimen, over 40% of the patients with TMC125 achieved this undetectability, which is the call of the treatment. Thirteen TMC125 resistance associated mutations were identified but in the presence of 01 [misspelled?] or even 2 of these mutations, there was still a virological response greater than the overall placebo and of note again, these three mutations were infrequent since its side effect only less than 15% of the patients. With regard to the tolerance of the drug, except for the rash, the incidence and severity of adverse events were really similar to the placebo. So I think we can really see TMC125 following these phase III studies and realize that this drug has the ability to extend and enhance the NNTI class, which is what we need in the clinics and provide really a new treatment option for patients with a resistance to all unable to tolerate other NNTIs and I would like to end by thanking, but very deeply thanking all the people, all the investigators, and we are [misspelled?] each investigator, all the clinical persons, the nurses who have been extensively working to put this presentation in 10 minutes - Duet 1 and Duet 2. I would also like to thank the [inaudible] people for their very scientific knowledge and thank you to be here [misspelled?]. Thank you very much.

[Applause]

HECTOR PEREZ, M.D.: Thank you Dr. Katlama. Microphone two?

MALE SPEAKER: A couple of little questions. Christine, congratulations for the presentation. The first was did you detect any case of rash that was associated with fever or with liver toxicity or all the cases were just skin involvement exclusively?

CHRISTINE KATLAMA, M.D.: The cases were very usually macular rash that disappeared. There was no, I mean, the cases you mentioned are grade III or IV and there was only one grade III. So really it's not - neither in the case of light [misspelled?] sensitivity. There was no thin [misspelled?] case. I think and again you know Josette [misspelled?] that I'm not having the 500 patients that - I think we - maybe more sure as to [inaudible] who knows even better than me that - so due [inaudible] any of the rash associated fever and transaminases.

MALE SPEAKER: So one percent of subjects had grade III rash but only two of the subjects were associated with rash with fever and there were no associations with increased liver transaminases in association with rash?

CHRISTINE KATLAMA, M.D.: So it's only 2 out of more than [inaudible] patients.

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

MALE SPEAKER: The second question, Christine, is when you related the degree of response with baseline mutations, did you consider only those mutations were actually present at baseline or you considered also those mutations [inaudible], and were detected before starting the trial?

CHRISTINE KATLAMA, M.D.: I think it was considered, the mutation that was present at screening and baseline before being enrolled and screened, you have to have mutations but there was no- I mean it could not be taken into consideration - the mutations that are in the past. Is that correct Mark [misspelled]?

MALE SPEAKER: So it was only those actually present at baseline - not those that might have been detected in the past but had disappeared at the moment?

CHRISTINE KATLAMA, M.D.: No because there was no centralization of that [inaudible].

MALE SPEAKER: Okay. Thank you.

HECTOR PEREZ, M.D.: Microphone 2.

MALE SPEAKER: Christine, beautiful studies, great results. I just don't understand how you come to the conclusion based on the data presented that 181C mutation does not compromise the virological response because I don't think you can say that based on what you presented.

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

CHRISTINE KATLAMA, M.D.: Sorry [inaudible] if I have not been clear. It was a little fast - ten minutes to give all the things included in the studies but I didn't mean that 181C was not effective but [inaudible] this mutation was a lot. There was no decreased activity. Neither with 1 or 2. It's only when it's associated with more than two. This is why with 181C that there was a decrease.

MALE SPEAKER: No, I think you were clear in stating that but the comparator was actually all patients, correct or was it the patients without one-

CHRISTINE KATLAMA, M.D.: I was sure that somebody would ask this excellent question, so I think I have the answer. So the comparator was not [inaudible] but the patient - had [misspelled?] no NNTI mutation. Okay?

MALE SPEAKER: Okay. No - now I understand. Thanks.

CHRISTINE KATLAMA, M.D.: Sure. You are quick.

MALE SPEAKER: One question more and then microphone 1.

RICK KULICK: Rick Kulick [misspelled?] from New York. Christine, thanks for the presentation. The results certainly are impressive but why do you think the people with a baseline PSS of three did no better than the groups with the PSS of two and wouldn't we like to see even higher response rates below 50 as we add additional active drugs?

¹ kaisernetwork.org makes every effort to ensure the accuracy of written transcripts, but due to the nature of transcribing recorded material and the deadlines involved, they may contain errors or incomplete content. We apologize for any inaccuracies.

CHRISTINE KATLAMA, M.D.: First, consider it's less than 50 at week 24. I'm sure you do not capture all - the entire, I know that patients enroll with - really high viral load, you cannot expect less than 50 so maybe over time, this may be changed. This is the first start of the [inaudible]. Otherwise, I would say but when you have many and several potential agents [misspelled?] and realize that the placebo, the control group is darunavir and when you have specifically darunavir and [misspelled?] T20, in the very highly resistant patient, because you know, T20 was not one of mine so it's always, most of the time, given in the most severely affected patients and in that case, at 24 weeks, you don't see anything expressed. It would be nice to go and [inaudible] to see if this population is not the one with the most, the highest number of resistance mutation but I think the simple message we can keep in the clinic is that when you have already 2 strong agents, 114 and 125, for most of the case if no active background, it's already given very, very excellent response - less than 50 copies.

HECTOR PEREZ, M.D.: Well thanks Christine and thanks [inaudible] on the speakers and the closing ceremony is coming.
[Applause]

[END RECORDING]