violation.

Patients could have one, two, three or even up to four protocol violations. So we closely examined the type of violations that had happened. We categorized the kinds of protocol violations into: screening or entry criteria violations; treatment violations of the regimen during the study; and other violations with use of prohibited concomitant medications.

The third category was much smaller, so we focused on the first two categories.

[Slide.]

About one-third of patients in both groups had screening violations. Examples of these were: no protease gene mutations at the protocol-specified codons; less than two PIs or less than three months of treatment on historical therapy; and screening viral load was below 1,000 copies--and so on.

[Slide.]

Again, about a quarter of patients in both groups had treatment regimen violations, such as

use of dual-boosted PIs--which was not allowed in the RESIST studies. If patients were randomized to a given protease inhibitors, then they took a different one, and patients remained on failing regimen because they did not get any new or recycled antiretroviral drugs in their background regimen.

[Slide.]

As you may recall, patients in the comparator protease inhibitor group had an escape clause. If the viral load had not dropped by a half-log after eight weeks of treatment, and they did not achieve a viral load below 100,000 copies, then they may discontinue the study and go to rollover study, .17, to receive tipranavir.

This escape clause was of concern as a possible source of bias in evaluating efficacy at Week 24. Even though our analysis counted as failures patients in both arms who met the criterion for escape at Week 8, there were more patients in the control group who had discontinued early.

Thus, the Committee may want to consider whether these early failures may reflect that patients were deliberately non-compliant with the

control regimen.

[Slide.]

The primary efficacy endpoint at Week 24 was the proportion of patients who had a confirmed 1-log drop in viral without having any evidence of previous treatment failure. And if any of these following events occurred during the study, the patient would be considered a treatment failure at Week 24.

So, Week 24 efficacy evaluation, this definition of a virologic endpoint of 1-log drop in HIV RNA is considered a reasonable surrogate endpoint because of the nature of the advanced disease status of the patient population.

Our analysis differs from that of the applicant in that we wanted to account for the potential source of bias due to escape clause at Week 8 in the comparator protease inhibitor group. So we changed the analysis by regarding all

patients who did not have a sustained half-log drop in HIV RNA through Week 8 and viral load below 100,000 copies as a virologic failure.

If patients did not have this event or any other pre-designed event of treatment failure, then that patient had a confirmed 1-log drop in HIV RNA at Week 24, and they were considered as responders.

The proportion of responders in RESIST 1 was 41 percent in the tipranavir group, and 21 percent in the comparator group. And in RESIST 2 it was 40 percent in the tipranavir group, and 14 percent in the comparator group. And these treatment differences of 20 percent and 26 percent were both statistically significant.

The major source of difference was due to the virologic failure, and specifically due to the category of "initial lack of virologic response at Week 8."

As you can see, not surprisingly, there were a greater number of initial virologic failures of no half-log drop in HIV RNA in the comparator PI group than in the tipranavir group. Recall that

the majority of the patients were "possibly resistant" or "resistant" to the pre-selected un-boosted PIs at baseline, and were now taking the boosted PIs.

The other failure categories were either balanced in both treatment groups, or they were numerically much smaller.

[Slide.]

We performed further sensitivity analyses on the efficacy data to address all those sources of potential open-label biases that I mentioned before.

The bias at Week 8 due to initial virologic failure was addressed in the intent-to-treat analysis. Upon further examination, we found that if a patient did not achieve a sustained half-log drop in the first eight weeks of treatment, then their chances of responding later--by Week 24--was very small. So it was only .5 percent in the tipranavir group that was a probability of responding later if they failed initially, as one 1.5 percent in the

comparator group if they failed initially, before Week 8.

We also did sensitivity analyses addressing the biases due to the mismatched T-20 stratum, and we did protocol analyses, adjusting for protocol violations that occurred among 50 percent of the patients.

[Slide.]

In the ITT analysis, we addressed the issue about the escape clause at Week 8. And after combining the results of RESIST 1 and RESIST 2, we see a net treatment benefit of 22 percent in favor of tipranavir.

The next analysis adjusted for the wrong T-20 stratum. In the tipranavir group, if patients were not assigned to take T-20 but they took it, then they improved their chance of success with two new drugs. Therefore, they were converted into treatment failures.

In the control arm, if patients decreased their chance of success and still responded, then they were considered as responders. But if they

increased their chance of success, then they were censored.

With this sensitivity analysis, the treatment effect of tipranavir was reduced to 18 percent, and the confidence intervals were shifted lower.

The treatment effect based on the per-protocol analyses of excluding either the treatment regimen violations of screening violations was similar to the original ITT analysis. This indicated that the treatment effect in favor of tipranavir was held, and is likely to range between 13 percent and 29 percent.

[Slide.]

Next we will present subgroup analysis based on the protocol-defined stratum of T-20, and the second stratum defined in the protocol was a pre-selection of the comparator protease inhibitors, which we have modified slightly.

[Slide.]

The first subgroup analysis is based on the T-20 use stratum. And since the results were

similar in both RESIST 1 and 2 trials, we have pooled the two studies and showing an analysis comparing tipranavir to the comparator PI group.

When patients used T-20 along with the assigned treatment, the treatment difference was 29 percent. And when T-20 was not used, the treatment difference was 16 percent. Therefore, tipranavir was superior to the comparator PIs in both T-20 strata.

One should also note that these two differences are statistically significantly different, which implies that for these advanced patients, introducing two new drugs--like tipranavir and T-20--confers a greater benefit than using tipranavir alone.

[Slide.]

The second subgroup analysis is based on the protocol-defined strata of pre-selected protease inhibitors. During our review of the data, we noted that even among nominally susceptible subjects, a substantial fraction of patients had prior exposure to the comparator

protease inhibitors.

In order to compare the performance of tipranavir to each of the control PIs, we subdivided each control PI stratum into three substrata: those who are both susceptible and naive to the control PI; those who are susceptible but have at least one month of prior exposure or more; and those who are "possible resistant" or "resistant."

[Slide.]

We found in the results--not presented here--that the experience level for the susceptible experienced group was usually at least six months; and the success rate at six months for the experienced susceptible and resistant groups were similar. Therefore, we pooled these two groups together for our analysis.

In addition, we found that the sample sizes in the susceptible naive groups were much smaller, and therefore we pooled results from both trials together.

So, based on our new definition, we have

combined the data from RESIST 1 and RESIST 2. And this graph clearly shows that at baseline, the number of patients who are "susceptible naive" and those who are "susceptible experienced" is much smaller than the group that is considered "resistant."

The largest protease inhibitor stratum for both studies combined was lopinavir, followed by amprenavir, saquinavir and indinavir.

[Slide.]

Next we will show efficacy analysis on a head-to-head comparison of tipranavir versus each comparator protease inhibitor in the subgroup of patients mentioned.

In this graph we are showing two panels showing statistical variability in the estimates of the treatment effect. The first panel shows results for patients who are susceptible naive, and have been randomized to tipranavir or the comparator protease inhibitor.

The second panel shows results for the group of patients who are either previously

experienced with a protease inhibitors or resistant to the PI.

If you look at the treatment difference for, say, lopinavir, it is much smaller and not statistically significant in patients who are susceptible and naive. This treatment difference gets larger for patients who are experienced or resistant. The same pattern is true for amprenavir--going from here to there.

The other noticeable thing in this graph is that the sample size in the susceptible naive patients is very small--which was shown in the previous slide. And although the point estimate on the treatment difference is slightly positive, the confidence intervals on the treatment differences are clearly very wide when comparing tipranavir to the protease inhibitors when these are active.

And therefore, on a head-to-head comparison basis, the evidence of significantly greater benefit with tipranavir is clear when patients are experienced or resistant with other protease inhibitors. However, the evidence of a

superiority claim for tipranavir versus other protease inhibitors is not convincing among susceptible naive patients.

When the comparator PIs are sub-optimal, the treatment effect is statistically significant and in favor of tipranavir.

[Slide.]

In summary: based on the collective evidence from the RESIST trials, the FDA analysis confirmed that tipranavir was statistically significantly better than the control with respect to the surrogate endpoint of percent with at least 1 log decrease in viral load at 24 weeks.

The efficacy of tipranavir boosted with ritonavir was shown when the best available comparator PI was sub-optimal.

We performed various sensitivity analyses that adjusted for the biases of the opportunity study design of the RESIST trials. And these results were consistent with the primary efficacy results. The net treatment benefit of tipranavir is likely to range from 13 percent to 29 percent.

[Slide.]

Efficacy of tipranavir was demonstrated regardless of the use of T-20, but the efficacy was

significantly greater when it was combined with T-20.

And boosted tipranavir is not shown to be better than any of the boosted PIs, such as boosted lopinavir or boosted or amprenavir or boosted saquinavir if patients are naive and not resistant to the respective protease inhibitors.

There was no data available to evaluate the efficacy of tipranavir against indinavir among patients who are susceptible and naive to indinavir.

[Slide.]

Finally, I'd like to thank my colleagues at FDA for their invaluable input during this challenging review.

And our next speaker will be Dr. Lisa Naeger.

Resistance Evaluation

DR. NAEGER: Good morning. I'm Lisa

Naeger, the Microbiology Reviewer for the tipranavir NDA. I'll be presenting the resistance analysis that was carried out by myself and Dr. Kim Struble.

[Slide.]

Tipranavir-resistant viruses were selected by the applicant in in vitro passage experiments. In these experiments, mutations arose in the order shown in this slide. L33 and I84V were selected first, followed by the K45I mutation.

Viruses with these three mutations showed threefold decreased susceptibility to tipranavir.

Viruses with greater than 10-fold decreased susceptibility to tipranavir were detected after six mutations, and this included the first three plus I13V, V32I and V82L.

After 70 passages and nine months in culture, viruses with 10-PI mutations were selected that showed 70-fold decreases to tipranavir. Mutations in the protease cleavage site and transframe region were also observed at passage 39, and were maintained in subsequent passages.

[Slide.]

And examination of in vitro cross-resistance showed that 90 percent of viruses

resistant to other PIs had less than four-fold decreased susceptibility to tipranavir; and that tipranavir-resistant viruses selected in vitro with a 10-PI mutation shown in the previous slide were resistant to all currently available PIs except saquinavir, which showed a 2.5-fold decrease in susceptibility.

[Slide.]

Our analysis of tipranavir clinical resistance will be presented today in two parts. First, our analysis of virologic outcome to tipranavir treatment, based on baseline genotypic and phenotypic determinants. And then I'll present an examination of the mutations that developed on tipranavir treatment.

[Slide.]

First we explored the baseline genotypic and phenotypic determinants of success or failure to tipranavir treatment.

[Slide.]

Our analyses looked at three different endpoints: the primary endpoint, which was proportion of responders with confirmed 1-log decrease at Week 24; the median DAVG at Week 24; and the median changes in HIV RNA from baseline at

Weeks 2, 4, 8, 16 and 24.

We focused this analysis on the RESIST trials, although we recognized that the Phase II trials 51 and 52 provide additional supportive resistance information, especially for the more highly treatment-experienced population.

[Slide.]

We performed on-treatment analyses, and for the primary endpoint we did not include in our data set subjects who discontinued while suppressed; subjects who discontinued before confirmed suppression due to an adverse event or other reason; and subjects with no Wee 8 to 24 HIV RNA data. And we also censored subjects who added any new antiretroviral or changed their PI. This gave us a data set of 1,015 isolates.

This approach for censoring and analyzing baseline resistance data is consistent with our draft guidance.

[Slide.]

For the DAVG Week 24 data set, we added back 300-plus RESIST 2 subjects who only had Week 16 at the time of submission. And this gives us a larger data set of 1,409 isolates.

[Slide.]

We examined virologic outcome by the number of baseline PI mutations, the type of baseline PI mutation, as well as the baseline tipranavir phenotype.

[Slide.]

First we assessed virologic outcome by the number of PI mutations present at baseline. In these analyses, any change at these 13 positions at baseline were defined by the FDA--I'm sorry, the 13 amino acids as defined by the FDA were counted if present at baseline.

Because subjects were stratified based on T-20 use, we examined virologic outcomes in three

separate groups: overall, those not receiving T-20, and those that received T-20 as part of their optimized background regimen.

Here we focus on the "no T-20" group in order to assess baseline resistance predictors of tipranavir virologic outcome without the additive effect of T-20 use on the overall response.

Response rates decreased as the number of PI mutations increased. But regardless of the number of baseline PI mutations, the tipranavir arm had approximately 20 percent more responders than the comparator arm, or the primary endpoint.

The response rates were reduced compared to the overall if there were five or more PI mutations present at baseline, with 28 percent that responded in the tipranavir arm, compared to 11 percent in the comparator arm.

[Slide.]

Using another endpoint--the median change from baseline of HIV RNA at Weeks 2, 4, 8, 16, and 24--we looked at the responses based on the presence of one to four baseline mutations, or five

or more in both arms.

An approximately 1.5-log decrease was seen at Week 2 for all subjects using tipranavir, regardless of the number of baseline PI mutations. However, in the tipranavir arm, those with one to four mutations--shown in red--has a sustained viral load decrease through week 24, while those with five-plus--shown in yellow--began to lose antiviral activity between Weeks 4 and 8; whereas the comparator arm at Week 2 had approximately a 1-log decrease for those with one to four baseline PI mutations--shown in green--and a less than .5-log decrease for those with five or more in the comparator arm.

[Slide.]

Similar results were seen to the overall results in the subjects not receiving T-20. Subjects who received tipranavir without T-20 and who had five or more baseline PI mutations--again shown in yellow--began to lose antiviral activity between Weeks 4 and 8.

[Slide.]

And subjects receiving both tipranavir and T-20 had a sustained viral load decrease of 1.5 to 2 logs through Week 24, even when there were five

or more baseline PI mutations--shown in yellow; and there was an approximately 1.5-log greater decrease compared to those that had five or more PI mutations in the comparator arm--shown in blue.

[Slide.]

We next examined virologic outcome by specific baseline PI mutation.

Virologic responses were analyzed by the presence at baseline of different protease amino acids. And we looked at greater-than-25 amino acids in the protease. We used both the primary endpoint and DAVG24.

[Slide.]

We show here results of the PI mutations that are present at baseline, had reduced virologic responses to tipranavir by the primary endpoint.

The reduction in virologic responses for these baseline substitutions was most prominent in the "no-T-20" group. Reduced virologic responses

were seen when there was a baseline substitution at I113, V32, M36, I47, Q58 or D60.

These response rates were 20 to 30 percent, compared to the overall 40 percent, with only 18 percent responding if they had an I47 V or A present at baseline. This consistent with the Boehringer Ingelheim results. These mutations that we found in our analysis that decreased the response to tipranavir are included in the mutations that they use in their tipranavir score.

[Slide.]

In addition, reduced virologic responses were seen in Tipranavir-treated subjects when isolates had a baseline mutation at I84. Virologic responses to substitutions at position V82 varied depending on the substitution.

In looking at any change at this position, there is no difference between the response rates and the overall. However, when we look at specific changes at this site, if there was a change at V82 of S, F I or L, only 15 percent responded, whereas those with an A, T or C at baseline had similar

response rates to the overall.

However subjects with both substitutions at V82 and an I84V mutation had lower response rates than the overall response, with response rates at 25 percent. And this was regardless of the change at V82.

Interestingly--and now shown in these tables--Tipranavir-treated subjects did better than the overall response if their isolates had a G48 substitution at baseline. And this was true even if they had four or more mutations.

[Slide.]

Next we examined tipranavir response rates by baseline tipranavir phenotype.

[Slide.]

Again we focus on the "no T-20" group. With no T-20 use, the proportion of responders was 45 percent if the fold change in tipranavir IC50 value from reference was three-fold or less at baseline.

The proportion of responders decreased to 21 percent when the tipranavir baseline phenotype

values were greater than 3 to 10; and 0 percent when baseline phenotype was greater than 10.

Please note that these baseline phenotype groups are not meant to represent definitive clinical susceptibility breakpoints for tipranavir, because it is based on this select patient population of the RESIST trials.

[Slide.]

By the DAVG endpoint and no T-20 use, subjects had greater than 1-log decrease if the fold change was 0 to 3; and less than .5-log decreases if it was greater than 3.

[Slide.]

Now, examining the mutations that developed on tipranavir treatment.

[Slide.]

In the RESIST trials, the most common mutations that developed in greater than 20 percent of the 59 tipranavir-failure isolates submitted with the Week 24 data were V82T, I84V and substitutions at L33 and L10.

The other mutations shown in this table

developed in 10 to 20 percent of the tipranavir-failure isolates. Many of these protease mutations that developed in these failure isolates are the same mutations that arose in the serial in vitro passage experiments.

Tipranavir resistance developed in these failure isolates on an average of 38 weeks, with an average decrease of 34-fold in tipranavir susceptibility.

The V82T mutation developed frequently--in 34 percent of the isolates--especially when the V82A mutation was present at baseline; whereas isolates with the wild-type V82 most often developed at V82L.

[Slide.]

To summarize our resistance presentation: tipranavir has antiviral activity against multi-PI-resistant clinical HIV-1 isolates. The most common protease mutations that developed--in greater than 20 percent of the isolates who failed on tipranavir treatment were: substitutions at L10,

I113, L33, M36, V82T or L, and I84V. The resistance profile in treatment-naive subjects has not yet been characterized.

[Slide.]

Virologic response rates in Tipranavir-treated subjects were reduced when: isolates with substitutions at positions I13, V32, M36, I47, Q58, D60 or I84, and substitutions V82S, F, I, L, as well as I47, had reduced response rates of less than 20 percent; and also combinations of substitutions at V82 with I84 had lower response rates of 25 percent.

Virologic response rates were also reduced when the number of baseline PI mutations was five or more. However, subjects taking both T-20 and tipranavir were able to achieve greater than 1.5-log reductions in viral load through weeks 24--even when they had five or more baseline PI mutations. And response rates were also reduced to tipranavir when the baseline phenotype for tipranavir was greater than 3.

Through evaluation of multiple endpoints,

irrespective of using a censored data set, consistent observations were made in each of the analyses conducted. These observations included that there were 20 percent more responders in the tipranavir arm compared to the comparator, and there were greater reductions in viral load in the tipranavir arm versus the comparator arm by both DAVG and median change from baseline.

So now I'd like to introduce Dr. Jenny Zheng who will discuss exposure-response analyses.

Exposure-Response Data

DR. ZHENG: Good morning. My name is Jenny Zheng. I will be presenting exposure-response analysis as rationale for tipranavir therapeutic drug monitoring.

[Slide.]

This analysis will demonstrate the measurement of tipranavir drug concentration in the viral IC 50 could be an option for individualization of tipranavir/ritonavir dosing.

[Slide.]

Let me first explain this figure: y-axis

in this figure is percent responder. "Responder" is defined as patients who had at least 1-log viral load reduction at Week 24; x-axis is inhibitory quotient, which is defined as the ratio of tipranavir trough concentration to corrected viral IC 50.

The relationship between percent responder at Week 24 and inhibitory quotient was examined. Data from patients who had both tipranavir trough concentration and IC 50 value in RESIST 1 and 2 studies were analyzed.

The dashed line represents the relationship between percent of responders to inhibitory quotient when tipranavir was used with T-20.

The blue line represents the relationship between responders and inhibitory quotient when tipranavir was not used with T-20.

The green actually is the result from the Phase II study.

The true solid line here represents the mean response rate in the control arm, with or

without T-20. According to the rank of inhibitory quotient, patients are divided into six groups: the observed response rate at the median inhibitory quotient in each group is presented as a symbol in this plot.

It shows that the model reasonably describes the observation.

I would like to make three points from this analysis. First, the response rate is related to inhibitory quotient. Increasing inhibitory quotient increased response rate in both situations: when tipranavir was used with T-20, and tipranavir was not used with T-20.

The second point is the treatment you use significantly increases response rate, which is demonstrated by the separation of dash line and solid line. For example, inhibitory quotient of 100, the response rate is increased from 36 percent to 63 percent, as compared with tipranavir if given alone.

The third point is that after the fixed dose of 500 mg tipranavir/200 mg ritonavir,

patients with low inhibitory quotient had a low response rate, especially when tipranavir was not used with T-20.

[Slide.]

In this observed the data set, when inhibition quotient greater than 100, 50 percent of patients responded to tipranavir itself, and 33 percent of patients responded to tipranavir plus T-20. However, when inhibition quotient is less than 100, only 21 percent of patients responded to tipranavir alone, and 52 percent of patients responded to tipranavir plus T-20.

This analysis indicates that monitoring tipranavir trough concentration and viral IC50 could be useful to optimize the treatment for individual patients--especially for the patients who have low inhibitory quotient.

Individualizing tipranavir dosing regimen to patient's need is an optional alternative to treating all patients with the same dose regimen.

[Slide.]

The steady-state trough concentration of

tipranavir from Phase II and Phase III studies are presented in this slide across different doses. Two points need to be made.

First, tipranavir trough concentrations are variable after fixed dose from Phase III study. This implies that patients who have unnecessarily high exposure might lead into toxicity. On the other hand, patients who have low concentrations are less likely to respond.

The second point is: tipranavir exposure was increased when tipranavir dose was increased. It implies that when it is needed, the tipranavir exposure can be increased by increasing tipranavir dose.

[Slide.]

This slide shows the distribution of inhibitory quotient from Phase II and Phase III studies. The inhibitory quotient displays even high between-subject variability. Because we know viral response is relating to inhibitory quotient, and inhibitory quotients are very variable after fixed doses, the response could be very different

among patients after the fixed dose.

Therefore, to optimize patients' response, inhibitory quotient for each patient needs to be measured, and dose needs to be adjusted accordingly.

For patients who need higher dose, their dose increase needs to be guided by individual tolerability. So qualitative analysis of relationship between toxicity and a response can be useful for guiding this dose selection for the patients who need higher doses.

[Slide.]

The association of ALT elevation and the drug exposure has been examined for Phase II study. It was found that ALT elevation is also related to tipranavir concentration. To minimize ALT elevation, tipranavir concentration should be measured and constrained to acceptable range.

What I have shown now is a fixed dose of 500 mg tipranavir/200 mg ritonavir results in variable exposure which could be translated into unpredictable viral response and ALT elevation in

the individual patient, unless the exposure and the viral susceptibility are measured.

[Slide.]

Based on that, a TDM strategy is proposed. And we would like to seek your feedback on the overall objective and the means of implementing it.

By this proposal, patients will start with 500 mg tipranavir/200 mg ritonavir dose. The IC 50 will be measured at baseline, and tipranavir trough concentration measured some time between Week 1 and 3. If inhibitory quotient greater than 100, the dose is tolerable, patient will be continued on the dose of 500 mg tipranavir/200 mg ritonavir. If inhibitory quotient is less than 100, patient is tolerant to the dose, a dose increase should be considered. If inhibitory quotient greater than 100, the dose is not tolerable, dose reduction could be considered. For the patients who have less IQ ratio less than 100 also is not tolerant to the dose, alternative treatment needs to be considered.

[Slide.]

I would like to revisit this slide in order to make our recommendation, which is: individualize dose according to patient's

inhibitory quotient and the trough concentration could be optimal alternative to treating patients with the same dose. The dose could be determined from this analysis, based on desired outcome and susceptibility of toxicity. Further confirmation of value of this paradigm needs to be made.

In summary, tipranavir exposure at it related to viral susceptibility is related to 1-log viral load reduction at Week 24. We would like the Committee's feedback on the use of inhibitory quotient and the tipranavir trough concentration for the individualization of tipranavir dosing.

I will introduce the next speaker, Dr. Zhang, who is going to talk about drug-drug action.

Drug Interactions

DR. ZHANG: Good morning. I am Derek Zhang. I'm going to present to you drug interaction findings for tipranavir in combination with low dose of ritonavir.

[Slide.]

In general, we concur with the sponsor's drug interaction study results, and the related recommendations. In this presentation, I'd like to bring your attention to the complexity of drug interaction that's difficult to predict.

First, I will review potentials for tipranavir/ritonavir to alter concentrations of other drugs; and the potential for other drugs to alter tipranavir/ritonavir concentrations.

Then I will discuss some examples of drug interactions that are difficult to predict. And I will conclude with a question for the Committee to consider.

[Slide.]

Potential for tipranavir/ritonavir to alter concentrations of other drugs--our in vitro drug metabolism studies demonstrate that tipranavir is CYP 3A inducer and inhibitor. The in vitro also demonstrates the inhibitory effects of tipranavir on other P450 enzymes: 1A2, 2D6, 2C9 and 2C19. However, whether tipranavir induces these P450

enzymes is not known.

In utilizing blood tests and in vivo measure of hepatic CYP 3 activity confirmed that in vivo, multiple doses of tipranavir alone induce hepatic 3A activity. However, the net effect tipranavir in combination with ritonavir on CYP 3A inhibition, because of ritonavir's inhibitory effect on CYP 3A.

The in vivo net effect of tipranavir/ritonavir on enzymes other than CYP 3A has not been evaluated.

Due to the known effect of ritonavir on 2D6, we anticipate potential net effect of tipranavir/ritonavir on 2D6 inhibition. The net effect of tipranavir/ritonavir 1A2, 2C9 and 2C19 is not known, due to ritonavir's counteracting effect on these enzymes, because ritonavir may induce 1A2 and 2C9.

[Slide.]

In vivo data from four studies submitted to the NDA demonstrate that tipranavir is P-gp inducer. And the net effect of

tipranavir/ritonavir on P-gp is induction--although ritonavir is a P-gp inhibitor.

The reviewed information allow us to draw conclusions regarding potential for tipranavir/ritonavir to affect other drugs. We know tipranavir/ritonavir inhibits 3A; in other words, administration of tipranavir/ritonavir can increase plasma concentration of drugs metabolized by CYP 3A.

In vitro, both ritonavir and tipranavir inhibit 2D6. Thus, tipranavir/ritonavir likely inhibits 2D6, and it may increase concentrations of drugs that are metabolized by 2D6.

However, the effect on 1A2, 2C9, 2C19 is not known.

[Slide.]

Tipranavir/ritonavir's net effect on P-gp is induction. And administration of tipranavir/ritonavir can decrease plasma concentrations of P-gp substrates. For example, we expect that tipranavir/ritonavir to decrease digoxin's concentration, because digoxin is P-gp

substrate. However the net is that due to 3A and the P-gp substrate is difficult to predict, because of the competing effects of tipranavir, ritonavir, 3A and the P-gp.

By inhibiting intestinal 3A, we expect the concentrations of 3A substrates to increase. However, by inducing intestinal P-gp, we expect the concentrations of P-gp substrates to decrease.

Thus, the net effect will vary depending on the relative affinity of the co-administered drug for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism effects.

[Slide.]

Two drug interaction studies submitted to the NDA exemplify this complexity. Atorvastatin is a dual substrate of CYP 3A and P-gp. Tipranavir/ritonavir increases atorvastatin concentration five to nine-fold. CYP 3A seems to be dominant for atorvastatin's absorption. Protease inhibitors amprenavir, lopinavir, saquinavir are also dual substrates of CYP 3A and P-gp. Tipranavir/ritonavir decreases

ritonavir-boosted PI concentrations by 50 to 80 percent. P-gp seems to be dominant for absorption of these boosted PIs.

I'd like to point out that there are many drugs covering a wide range of therapeutic areas are dual substrates of CYP 3A and P-gp.

[Slide.]

Now, I'd like to discuss potential for other drugs to alter tipranavir/ritonavir.

Our in vitro studies demonstrate that tipranavir is a 3A substrate, and that 3A is a major enzyme involved in the tipranavir metabolism. The in vitro studies also demonstrate tipranavir is a P-gp substrate.

[Slide.]

Thus, we can predict co-administration of tipranavir/ritonavir and drugs that induce 3A and P-gp may decrease tipranavir plasma concentrations.

[Slide.]

We also concluded that co-administration of tipranavir/ritonavir and drugs that inhibit 3A may not further increase tipranavir plasma

concentration. This conclusion is supported by the results of a multiple-dose tipranavir/ritonavir PK study with C14-labeled tipranavir. At the steady-state, unchanged tipranavir was predominant, and accounted for about 99 percent of the total plasma radioactivity--suggesting there is no room for further inhibition of metabolism.

[Slide.]

We also conclude that co-administration of tipranavir/ritonavir and the drugs that inhibit P-gp may increase tipranavir plasma concentrations. Two drug interaction studies submitted in NDA support this conclusions.

Fluconazole and clarithromycin can inhibit P-gp. But tipranavir concentrations increased 40 to 100 percent by fluconazole and clarithromycin--likely due to P-gp inhibition.

[Slide.]

Now I'd like to highlight some examples of drugs that are likely to be co-administered with tipranavir/ritonavir, but tipranavir/ritonavir's effect on these drugs are unknown.

Anticoagulant warfarin is a 2C9 substrate. We cannot predict the effect of tipranavir/ritonavir on warfarin, due to competing

effects of tipranavir and ritonavir on 2C9.

And many calcium channel blockers are dual substrate of CYP 3A and P-gp. We cannot predict the effect of tipranavir/ritonavir on them, because of competing effects of tipranavir/ritonavir on 3A and P-gp.

And for anti-diabetic agents, glitazones are metabolized by 2C8, which is a newly emerging enzyme. We don't know the effect of tipranavir on 2C8. And sulfonylureas are metabolized by 2C9. Interaction is possible but difficult to predict.

[Slide.]

So, given the unknown net effect of tipranavir/ritonavir on P450 enzymes 1A2, 2C9, 2C19 and 2D6, and given the competing effects of tipranavir/ritonavir on 3A inhibition and P-gp induction, we would like to ask the Committee what additional drug interaction information is important for the safe use of tipranavir/ritonavir

in the target population.

Thank you.

And our next speaker is Dr. Andrea James.

Safety Profile and Conclusions

DR. JAMES: Good morning, everyone. We're in the final stretch--so hang on.

My name is Andrea James, and I am the Primary Medical Reviewer for the tipranavir New Drug Application. This morning I will be presenting to you the FDA's safety analysis.

[Slide.]

This first slide is an outline of my presentation. I will begin by briefly summarizing the safety data that I reviewed, and the limitations of that data.

I well then go on to discuss three tipranavir-related safety concerns: namely, hepatotoxicity, rash and hyperlipidemia--followed by what we were able to assess about clinical progression events in the RESIST trials.

I will wrap up my presentation with a summary of the major risks and benefits associated

with tipranavir use, and then a preview of the questions we would like the Advisory Committee members to focus on this afternoon.

[Slide.]

The data I reviewed and am about to present was part of the original NDA submission that came in December 2004, and covers the tipranavir development program through June 11, 2004.

In February 2005, BI submitted the NDA Safety Update, which covers the tipranavir development program through September 30, 2004. The safety presentation by BI's Dr. Corsico was based on the NDA Safety Update data. The NDA Safety Update was submitted to the FDA as a clinical study report, and not as raw data. Therefore, I cannot independently verify the data, nor include it as part of my presentation.

The good news is that the NDA's Safety Update Study report confirms and strengthens the safety signals identified in the original NDA submission. Additionally, no new signals were

identified in the NDA Safety Update. So, although the numbers in my presentation may differ from that of Dr. Corsico's, the message should be consistent.

[Slide.]

I'll begin with the safety summary.

Dr. Corsico just gave a very detailed presentation on the safety of tipranavir, so I am not going to go into any detail regarding the adverse event profile of tipranavir I'm projecting this slide to point out two things.

One, although tipranavir was superior to the partially active comparator arm from a viral load standpoint, from the safety standpoint were slightly more AEs, SAEs, and AEs leading to discontinuation on the tipranavir arm versus the comparator arm.

The other point to note on this slide is that although the arms appear to be comparable for Grade 3 and 4 adverse events, investigators in the RESIST trials did not collect Grade 3 and 4 clinical adverse events discretely; rather, they were collectively captured as "severe events," and

therefore we cannot be certain what portion of these AEs are actually due to severe Grade 3 AEs versus what portion are due to life-threatening Grade 4 AEs--and consequently, if there is any difference between the two arms with respect to Grade 3 and 4 clinical events.

[Slide.]

Next I will take you through the tipranavir safety concerns, starting with hepatotoxicity.

[Slide.]

This slide presents the DAIDS toxicity grading scale used, and the range of upper limits of normal for ALT and AST in the tipranavir clinical trials. I'd like to highlight that Grades 3 and 4 events exceeded 5 to greater that 10 times the upper limit of normal, and that there was a wide range of upper limits of normals used in the tipranavir clinical trials.

[Slide.]

The first--and probably most concerning--evidence of tipranavir-related hepatotoxicity is

seen in the 18 Phase I studies where 19 percent of healthy volunteers with normal LFTs at baseline had some level of drug-induced ALT elevation. The majority of these 13 percent were elevations above the upper limit of normal. However, 4 percent of subjects had Grade 3 ALT elevations, and 2 percent of healthy normals had Grade 4 ALT elevations.

The median time to onset for these ALT abnormalities was 16 days, with a range of six to 46 days.

[Slide.]

If we look at the definitive dose finding study--1182.52--where subjects received tipranavir/ritonavir at a dose of either 500/100, 500/200, or 750/200 mg, you can clearly see a linear relationship between the dose of tipranavir/ritonavir and the rate of treatment-emergent Grade 3 and 4 ALT elevations--with the rate doubling as you go from one dose to the next.

[Slide.]

In order to understand whether these ALT

elevations were related to tipranavir or ritonavir, the exposures of both tipranavir and ritonavir were compared across three doses. The trough concentrations, which are defined in this analysis as the observed concentrations between nine and 15 hours after the dose at Day 14 are shown in this figure.

Just to orient you: ritonavir is plotted on the left, and tipranavir is platted on the right.

If you look at the 750 mg/200 mg dose relative to the 500/200 dose you will see that the median ritonavir concentration is lower at 750/200 versus 500/200, and the median tipranavir concentration is higher.

These exposure plots are supportive evidence that the dose-related hepatotoxicity is an effect of tipranavir and not ritonavir.

[Slide.]

Moving on to the pivotal Phase III RESIST trials, you can see in this slide that, overall, there were more treatment-emergent hepatotoxicity

on the tipranavir arm--shown in orange--at 6 percent, versus 2 percent on the comparator arm--shown in blue.

[Slide.]

If we break it down into Grade 3 ALT, Grade 4 ALT, Grade 3 AST, we see that the same pattern exists for the greater proportion of subjects on the tipranavir arm--3 percent, to be exact--at Grade 3 and Grade 4 ALTs, and Grade 3 ASTs, as compared to the comparator arm, where Grade 3/4 ALT and AST elevations were seen at lower rates of 1 to less-than-1 percent.

Grade 4 AST and Grade 3/4 bilirubin were less common, and there did not appear to be a difference between the two arms.

From this point on in my presentation I will focus on transaminase elevations, as that was the cause of the vast majority of hepatotoxicity. So the numbers I will present will not include the few subjects with isolated hyperbilirubinemia.

[Slide.]

This figure represents the maximum range

of Grade 3 and 4 ALT and AST values seen on the two study arms. As you can see, tipranavir's maximum ALT values exceeded that of the comparator arm, with one subject having an ALT value greater that 35 times the upper limit of normal.

There is less of a difference in the AST maximum values between the two arms, with tipranavir having a few outliers.

[Slide.]

All of the 6 percent of subjects who experienced the treatment-emergent Grade 3 or 4 ALT or AST, 27 percent discontinued treatment as a result of that lab abnormality; whereas none of the subjects on the comparator arm with Grade 3 or 4 ALT or AST elevations discontinued due to their elevated transaminase.

Of the subjects with Grade 3/4 transaminase elevations, the majority of them--or 64 percent--resolved most of the time while remaining on therapy.

Most of the subjects with unresolved transaminase elevations were classified as

"unresolved" because their transaminase elevations occurred at the last capture-date of the study, namely at study discontinuation at Week 24. And, at this point, I'd just like to remind you again that I am reviewing the original NDA submission data.

So, at the time of the original NDA submission, there were no deaths either directly or temporally related to these transaminase elevations.

[Slide.]

In the RESIST trials, subjects with tipranavir-related hepatotoxicity presented asymptomatically, with a median time to onset of 56.5 days. The range of days was eight to 176, which encompasses the entire study assessment period of Week 1 to Week 24. So the risk period appears to begin from the time you start dosing tipranavir, and remains as long as you are dosing the drug.

[Slide.]

In an attempt to assess whether or not

there are baseline predictors of who might go on to develop tipranavir-related hepatotoxicity, we looked at baseline ALT, baseline AST, and baseline hepatitis status.

[Slide.]

In the RESIST trials, one of the inclusion criteria was having a baseline ALT or AST of less than or equal to Grade 1. However, there were approximately 3 percent of subjects on each of the tipranavir and comparator arms who had Grade 2 or higher ALTs or ASTs at baseline.

[Slide.]

If we look at the subjects with baseline ALT or AST greater than Grade 1, we see that on the tipranavir arm 0.5 percent of these subjects went on to develop a Grade 3 or 4 transaminase elevation, as compared to 2 percent on the comparator arm.

Overall, however, the number of subjects who fall into this category are too small to draw any conclusions regarding baseline ALT or AST as a predictor for hepatotoxicity.

[Slide.]

We then looked at having a history of hepatitis B or C as a potential risk factor for

developing elevated transaminases.

In this slide, the numerators represent the number of subjects on each arm who are Hepatitis B or C positive at baseline who then went on to develop a treatment-emergent Grade 3 or 4 transaminase. The denominators represent the total number of subjects on each arm with hepatitis B or C at baseline.

You can see, on the tipranavir arm, that 9--or 12 percent--of the 76 subjects with hepatitis B or C at baseline went on to develop hepatotoxicity while they were taking tipranavir. In comparison, only 5 percent of subjects with hepatitis B or C at baseline developed hepatotoxicity while on the comparator drug.

Thus, it appears that the risk of treatment-emergent hepatotoxicity in subjects with viral hepatitis at baseline is more than double in the tipranavir group versus the comparator group.

[Slide.]

On the other hand, this slide shows that having hepatitis B or C at baseline is not the only risk factor for developing hepatotoxicity, since only one-fifth--or 20 percent--of the tipranavir-associated hepatotoxicity can be

explained by having hepatitis B or C at baseline.

[Slide.]

So, to summarize the hepatotoxicity seen with tipranavir, transaminase elevations were common throughout the development program, with ALT elevations occurring more often than AST elevations; and these elevations were observed commonly in health volunteers as well as HIV-positive subjects.

Subjects present asymptomatically, and throughout the time they are on drug. The majority of the transaminase elevations resolved either on or off treatment; however, obviously, having patients with very high ALT values, even in the absence of symptoms, is treatment limiting.

Having hepatitis at baseline appears to be

a risk factor for developing hepatotoxicity, but is not the only risk factor.

And the best monitoring and management strategy is unclear at this time, but LFTs probably should be monitored early and often, since the injury appears early and all throughout the dosing period.

[Slide.]

The next safety concern I will speak about is rash.

The initial rash signal was seen in healthy female subjects in Study 1182.22, which was a drug interaction study of Ortho-Novum 1/25 and tipranavir.

[Slide.]

33 percent of subjects on this study developed rash, and an additional 18 percent of subjects had musculoskeletal symptoms, or symptoms consistent with hypersensitivity which led to the premature stopping of the study because of the concern that these women were experienced serum

sickness.

[Slide.]

This is an example of what this rash looked like. This picture shows a women with a macular plaque-like rash on an upper extremity.

[Slide.]

And this is another picture of a women with a macular-papular rash on her lower extremity.

[Slide.]

If you look at the chemical structure of tipranavir you will note that tipranavir is a sulfonamide. Although tipranavir does not have the classic sulfa drug structure of an aromatic unsubstitued amine substiuent pairs in the sulfonamide moiety, as seen in this cartoon of sulfamethoxazole, it is still a sulfonamide, and therefore believed to have the potential for rash and hypersensitivity reaction in subjects who are sulfa-sensitive.

[Slide.]

As an example, both the RESIST trials and Study 1182.51 allowed enrollment of subjects with a

history of sulfa allergy, and approximately 18 percent of enrolled subjects in these studies had a known history of sulfa allergy.

On Study 1182.51, subjects with a history of sulfa allergy developed rash more frequently--at 17 percent--than subjects without a sulfa allergy--at 7 percent.

[Slide.]

However, in the RESIST trials, the rate of rash was the same, whether or not the subjects were identified as having sulfa allergy. So tipranavir's being a sulfonamide might explain some of why we saw such a high rate of rash in the health women, Study 1182.22, but it doesn't explain the whole picture.

[Slide.]

When we looked at the rest of the tipranavir development program, we saw that consistently females had a higher incidence of rash than males. In the Phase 1 trials, 13 percent of females versus 4 percent of males developed rash. In the Phase II trials we again saw that 13 percent

of females versus 8 percent of males developed rash. And the definitive dose finding study--1182.52--the data actually suggests that rash may be dose-related. In the arms where the dose of ritonavir was controlled--so the 500/200 mg dose and the 750/200 mg dose--but the tipranavir dose was increased, you can see that the incidence of rash increased from 4 percent to 15 percent.

[Slide.]

Looking at the RESIST trials, overall the frequency of rash was similar between the two arms: 11 percent on the tipranavir arm, versus 10 percent on the comparator arm. However, if you look at the women in the study who developed rash, you will see that the tipranavir arm had a higher rate at 14 percent, compared to 9 percent on the comparator arm.

[Slide.]

So, in summary, regarding rash: tipranavir is a sulfonamide and, based on the data we reviewed, we cannot rule out the relationship of the sulfa moiety to development of rash. Overall,

in controlled trials, rash is not more common on the tipranavir arms than the comparator arm. However, female subjects on tipranavir have a higher frequency of rash than their male counterparts. From Phase I to Phase III studies the rate is consistently 13 to 14 percent in female subjects. However, these findings are limited by the fact that these studies enrolled a relatively small number of women--only 12 to 16 percent of the study population being female--and therefore underpowered to draw any definitive conclusions about these findings.

We also still don't know why this finding seems to be specific to female subjects. We hypothesize, based on the data I just presented to you, that there may be an immune mediated component or a hormonal component, since the highest rate of rash--33 percent--was seen in healthy young women on birth control pills. But, of course, these theories require further investigation.

[Slide.]

The last safety topic of concern is

hyperlipidemia.

This slide is a reference slide that presents the DAIDS toxicity grading scale used for fasting triglyceride levels in the tipranavir clinical trials. It is important to note that a Grade 2 is where most clinicians would intervene because the risk of pancreatitis due to hypertriglyceridemia begins around 500 mg/dL.

[Slide.]

Here I project the rates of Grade 2 to 4 treatment-emergent hypertriglyceridemia. You can see that the frequency on the tipranavir arm is nearly double that of the comparator PI arm at every grade.

Please keep in mind that all of the PI regimens used in the RESIST trials were boosted by ritonavir, and therefore have the potential to cause hypertriglyceridemia. But the tipranavir arms do so at a much greater extent.

[Slide.]

This is a reference slide from the common toxicity grading scale used in the RESIST trials

for cholesterol. Again, I make reference to Grade 2 events because, clinically, this is where you would likely intervene with a cholesterol-lowering agent

[Slide.]

Here I project the percent of subjects with Grade 2 to 4 treatment-emergent hypercholesterolemia. Equally as striking as the slide on hypertriglyceridemia, you see that the incidence of treatment-emergent hypercholesterolemia on the tipranavir arm far exceeds that of the comparator arm.

[Slide.]

So, in summary, the tipranavir group has a much higher rate of hyperlipidemia than the comparator group: 46 percent of tipranavir subjects had Grade 2 to 4 treatment-emergent hypertriglyceridemia, versus 24 percent of comparator subjects; and 15 percent of tipranavir subjects had Grade 2 to 4 treatment-emergent hypercholesterolemia, versus 5 percent of comparator subjects.

[Slide.]

My last point of discussion for safety deals with clinical progression events. Although

we use viral load as a surrogate ep
for clinical benefit, we always look at potential clinical benefit by examining AIDS defining events and mortality. In the RESIST trials we're not really sure of the rate of AIDS defining events, because AIDS defining events were not collected by the methods recommended in the FDA guidance; which is to say they were not captured and assessed prospectively by a blinded adjudication committee. Instead, they were captured as part of the adverse event data and retrospectively defined by BI as being AIDS defining events.

In an open-label trial, with lots of potential for bias, this type of data collection and analysis is not reliable.

In terms of mortality, death rates for the two arms were equivalent at Week 24, at 2 percent.

[Slide.]

Some possible causes for the similar

mortality rates are: this was a very advanced population, so the natural course of the disease, or the impact of co-morbid diseases, or concomitant medications could all have affected the mortality rate.

We also need to consider the impact of the study design of the RESIST trials. These were open-label studies with an escape clause at Week 8 that led to the early loss of the control arm, and may have artificially made the mortality rate similar on both arms.

Additionally, the 24-week endpoint may be too early to detect a clinical benefit in terms of the difference in mortality rate--if one, in fact, exists.

[Slide.]

So, in conclusion, I would like to point out the overall risk and benefits of tipranavir use as presented by the FDA review team.

In the pivotal RESIST trials at Week 24, tipranavir was able to demonstrate superior activity over a suboptimal control group in a

three-class antiretroviral-experienced, clinically advanced HIV-1 infected population--especially when the resistance profile was favorable, namely having a tipranavir phenotypic score of less than 3, and having less than five PI mutations, and when tipranavir was used in conjunction with T-20.

However, the use of tipranavir is complicated by the multiple drug-drug interactions; the high inter-patient variability in tipranavir exposure--with that variable exposure, having potential safety and efficacy implications; and, lastly, the safety concerns of hepatotoxicity, rash and hyperlipidemia.

That being said, we believe that for this very advanced population with limited treatment options, tipranavir boosted by low-dose ritonavir can offer virologic and immunologic benefit, especially when combined with another active agent such as T-20.

[Slide.]

Lastly, I'd like to thank the entire tipranavir review team for all their hard work; but

specifically my colleagues DR. Melisse Baylor, Dr. Neville Gibbs, Dr. Rosemary Johann-Liang, Dr. Jenny Sheng, and Dr. Susan Zhou for their review and analysis of the supportive clinical trial data.

[Slide.]

I'm going to go on to briefly introduce the questions to the Committee before we take questions and clarification.

We'll be posing this afternoon--and we'll go into a little more detail this afternoon--seven questions.

Our first question is our standard question that we'll ask you whether the data that we've presented today demonstrates the safety and effectiveness of tipranavir. And then, based on your answer to that, we have some sub-bullets that we would like you to address.

[Slide.]

The next question asks you: given the data on the transaminase elevations, the patient population that you would use tipranavir in, and how you would monitor and manage those patients.

[Slide.]

The third question has to do with rash in females and asks you for recommendations on how to

best study this signal and investigate this signal.

[Slide.]

The fourth question asks that you comment on additional post-marketing drug interaction studies, given the unknown effect of tipranavir on multiple CYP enzymes.

[Slide.]

The fifth question has to do with the high inter-patient variability in tipranavir exposures, and asks that you discuss some studies that you would recommend to supplement the data that was presented today.

[Slide.]

The sixth question has to do with tipranavir resistance data, and how best to present that in package inserts for clinician use.

[Slide.]

And we will go through some examples for you.

[Slide.]

[Slide.]

[Slide.]

[Slide.]

And then the last question asks you to discuss and recommend future study designs for the

heavily pre-treated population.

DR. ENGLUND: Thank you very much. I'd like to thank the FDA for their presentation.

What I'd like to do now is emphasize to the Committee that the next hour or so we're going to spend--I want you to know the questions, but the next hour is really devoted to asking questions about the presentation of the sponsor and of the FDA. And we are not going to answer--or I'm not supposed to allow you to be asking questions that aren't directly in response to the presentation.

This afternoon we're going to discuss all these questions and really have more time specifically for the questions. But this is to discuss the data we've heard, the interpretation of the data.

And we're going to start first by asking questions for the sponsor. And we can request clarification by the FDA with these.

And, secondly, we will ask questions--if there are specific questions for the FDA.

So, at this point, we know what the questions are going to be this afternoon. We're going to discuss these points, question-by-question this afternoon, but this point is: please discuss

the slides that we have seen, and if we need clarifications or understanding with that.

Questions from the Committee to the Sponsor and FDA

DR. ENGLUND: So, at this time if you'd like to raise your hand I will try and--and I'm supposed to say: use the mike--of course.

So we'll start now. I'll try and get everybody. Try and make your questions relatively specific. We don't have lots of time today.

And I would just like to say that I'm excited about being able to answer Question No. 7 today. So that means that I'm going to be a little bit hard on everybody to get the questions

specific.

And please--do they need to identify themselves? Yes--either you or I have to identify you before you speak because it's being transcribed.

So--Dr. Grant.

DR. GRANT: Thank you very much. And congratulations to both organizations for outstanding presentations.

Clearly, differences in adherence could affect the interpretation of studies, especially open-label studies. And I'm wondering how adherence was measured in the RESIST trials; and, specifically, if pill counts were done, if there were differences in adherence measured by pill counts in the control PI arm versus the tipranavir arms.

DR. McCALLISTER: We did measure adherence through pill counts, and both arms actually had excellent adherence--more than 95 percent. And therefore there was no really ability to measure

those who had a different treatment response between non-adherent and adherent.

DR. ENGLUND: Ms. Dee?

MS. DEE: Yes--Linda Dee.

I am dismayed that there weren't interaction studies with methadone in more women in your studies. Can you tell me why an interaction study with methadone wasn't done. And why there weren't more women?

DR. McCALLISTER: Sure. Sure.

As a matter of fact, the methadone study has actually been conducted and clinically completed. And we have not yet reviewed the data with the FDA so it has not been presented.

But once reviewed with the FDA it will be shown.

MS. DEE: So, in other words why wasn't it done before Phase III, though? I mean, at this time point it would seem that that should have been done quite a while ago.

DR. McCALLISTER: Right. We performed, as you saw, a large variety of studies. And the

sequence of availability of that particular study happened to have just come during the Phase III program.

In terms of your second question, about women: we did make an effort to include women in the study through having 21 countries and 270 sites--as you saw in one of the earlier slides. We didn't make any specific actions at these individual sites to encourage them, though, beyond what they had available in their general population.

We did go to community clinics, university-based settings, and VA centers. And the combination of all of those gave us an approximation of women--as you saw--of about 15 percent.

I will say for our ongoing naive trial, we are conducting that in 15 countries, and the percentage of women that we have, at least so far, is higher. It's a little over 20 percent.

MS. DEE: And can--just one quick question: the number of tipranavir patients that still have

unresolved hepatic toxicity--and can you give us a clinical update on the number, or the percentage?

I mean, I don't have a good feel for how many people that is.

DR. McCALLISTER: Sure. My colleague from drug safety, Dr. Corsico, please?

DR. CORSICO: If you look at our RESIST data set through September 30, and you look at the Grade 3/4 elevations--

[Slide.]

I'd just like to bring up this next slide, which hopefully will put this in some kind of perspective and context for you.

[Slide.]

57 patients out of the 74 actually continued their treatment. And for the patients that continued, 47 of those did it without any interruption, which meant that the clinicians continued the therapy, no reason to interrupt therapy.

There are 10 of those 57, they interrupted. And following interruption, the

resolution over that period of time was on the order of approximately 27 days. They were then re-challenged.

Upon re-challenge, a majority of those patients actually did develop another Grade 3 or 4 elevation in their ALT, AST, but continued therapy because the clinicians felt that that was the best treatment option for the patient, despite those elevations.

For the patients that discontinued therapy--17--you can see, a majority of them actually were Grade 4. And, seven of them were Grade 3.

On a whole, that group that discontinued therapy had resolution of their liver function tests in approximately 19 days.

As noted earlier during my core presentation, there was one patient in the discontinuation group who actually was hepatitis B co-infected and did die. And that patient had CD4 counts of below 50, both at the time they started therapy, and a CD4 count that was measured closest

to the time of death.

DR. ENGLUND: Thank you.

Dr. Kumar?

DR. KUMAR: My questions are mainly related to safety. And I specifically want to ask a few questions about the hyperlipidemia.

Both your presentation, as well as the FDA presentation, went through the treatment-emergent both hypertriglyceridemia and hypercholesterolemia. And that's clear to me.

Is there any further information that you can provide in these patients that had Grade 3, Grade 4 hypertriglyceridemia and hypercholesterolemia, how they responded to lipid-lowering agents. And I want to add a line to that.

As clinicians, many of us recognize that it's a necessary evil, that they are going to have hyperlipidemia, especially when they're boosted with doses of ritonavir. But part about this thing, the risk benefit analysis, is will they respond to a lipid-lowering agent, especially when

there are drug interactions and you can't give them some of the lipid-lowering agents to the dose that we can give.

So I'd like to see what information you have in your data base that you could share with us.

DR. McCALLISTER: Dr. Corsico.

DR. CORSICO: Thank you, Dr. Kumar.

If I could show the next slide, please.

[Slide.]

We actually looked at patients who started lipid-lowering drugs at the time they were randomized into the trial. And you see no significant difference between the two treatment arms.

We then went to on-treatment and found that 17.4 percent of the tipranavir-treated patients, versus 10.7 percent of the comparator-treated patients actually started lipid-lowering drugs. And that was a statistically significant difference.

The next slide should show the result of

using lipid-lowering drugs in this patient population.

[Slide.]

And what you see is that the median triglyceride level in the comparator arm, before therapy, was 390, with the intra quartile range of 259 and 581.

After starting their CPI and lipid-lowering agent, the median triglyceride level of 355--again, intra-quartile range 230 to 538. Compare that to the tipranavir arm, where it was 445 for that triglyceride level, and then after starting therapy, 367.

We see a potential trend here, but we can't any definitive conclusions. But in order to help the current clinicians, I think this next slide, which shows a Kaplan Meier of the rate of rise of greater than 500 mg/dL increase in triglycerides is important.

[Slide.]

When you look at confirmed cases, where they maintain that greater than 500 over a period

of time, you see that the greatest period of risk is in the first four weeks. Therefore, careful monitoring during this period of time will allow you to identify those patients with that elevation of greater than 500.

Now, clearly, you as the clinicians have to understand the drug-drug interactions, and therefore we would recommend that you would do what you would do with any drug that potentially interacts via this pathway in terms of managing your patients.

DR. KUMAR: Can I ask a follow up question?

Just so that I can understand it better: do you have data on what percentage of your patients--like if you had somebody with a great fold hyperlipidemia--split up in the cholesterol and triglycerides, and they were started based on clinicians. I suspect that you didn't dictate what it was clinicians started.

What percentage of them went down from a Grade 4 down to Grade 3 or Grade 2 by the lipids.

DR. CORSICO: Unfortunately, at this point

we do not have that data available. You raise a very important point, and additional analyses that need to be done.

DR. ENGLUND: Dr. Fish.

DR. FISH: Two questions: the first question relates to the potential for sulfa allergy.

If a patient has a history of a severe sulfa reaction--say Stevens-Johnson--would tipranavir be contraindicated for that patient?

And the second question relates to drug-drug interactions that were noted with zidovudine and abacavir in particular, and to a lesser extent with didanosine.

Can you place the reactions--the decreases--that were seen in your studies in the context of other protease inhibitors, and the potential impact of the ritonavir component versus the tipranavir component leading to those decreases?

DR. McCALLISTER: With regard to your first question, about SJS and TEN, we didn't see any

evidence of that in our trials for patients that received tipranavir.

Regarding the zidovudine and abacavir in comparison, I'd like to call on my clinical PK colleague, Dr. Tom McGregor, please.

DR. McGREGOR: Good morning. I'm Tom McGregor from R&D. And if I could have slide 34.

[Slide.]

If we look at zidovudine, and we compare it to ritonavir, we see that there's an increase to about 43 percent in the area under the curve as a decrease in levels. This is comparable to something that you see with nelfinavir and in the label of noravir.

Didanosine, we saw a decrease of 10 percent--and this was about comparable to what is seen with ritonavir, but this is a very limited data set, in that this study was stopped prematurely. But we feel that if you separate--what we didn't do here was separate the didanosine from the tipranavir in administration. Remember that tipranavir is given with food, and

didanosine should not be.

And we feel if you separate the two, that this is about the reaction--the difference that you'll get.

And then, as far as abacavir, we did see a decrease. And in each one of these cases, what we think we're seeing is the decrease that you normally get with ritonavir, with perhaps a slight exacerbation due to P-gp efflux. But we're not quite sure if any of these drugs are--how much potential they have for P-gp efflux.

DR. ENGLUND: Dr. Haubrich.

DR. HAUBRICH: Yes, just a couple quick questions.

First, in slide 31, CD4 analysis in the control group, how were those patients handled in those that discontinued? How did you count the CD4?

And then two quick questions on the resistance analysis: why was an intent-to-treat analysis done? That sort of analysis is really exploratory, trying to look at resistance,

predicting response. You really don't care if patients dropped out because they moved to Tennessee.

And, along the same lines, all of the analyses presented by both groups, in my opinion, slightly suboptimal because they make no attempt to--except for the subgroup analysis the FDA did--for accounting for the other drugs in the regimen.

The ideal study to come up with genotype or phenotype cut points would rely on using data sets where a single drug is added in. In the absence of that, then some attempt should be made to try to account for the effects of the other drug in the regimen.

DR. McCALLISTER: Regarding your first question, about CD4 count, those were ITT analyses that were conducted--on that slide.

DR. HAUBRICH: So if they dropped off in the control arm they were treated as having zero CD4 rise?

DR. McCALLISTER: It was the last value

that they had on the time of treatment.

For the resistance questions, my colleague Dr. Mayers, please.

DR. MAYERS: Why we did an ITT analysis is because that's what we did. Sorry, Rich.

I think, you know, it gets a little tricky deciding who to censor and how to censor in such a way that you don't advantage your drug versus another drug. And we just chose to use ITT as the most non-biased analysis. You are right, though. We do include some outliers; patients who probably didn't contribute to the response.

Regarding the score, we actually do have data, because from that Phase II study, where I had functional monotherapy, we actually did do the tipranavir score with the functional monotherapy patients as well. So it correlates a good bit--the functional monotherapy, with the RESIST studies.

The real problem was is that if you look at the RESIST studies--and I think I'd like to show slide 6, because I think this is an important confounder of the resistance data.

And one of the problems that we have in looking at this data--

[Slide.]

--yes, there we go--is that as you look at the number of patients who have less than one background drug--so one or less background drugs in your regimen--as these scores go up, you end up with two-thirds of the patients in the arms having one or less background drugs to support your drugs. You end up in almost functional monotherapy across many of these arms. And that confounds all these durability analyses that we're trying to do.

But, in essence, the answer is that even when they were told it was genotypically susceptible, it as often high level ACT resistance, with a report reading "susceptible for d4T, ddI, or ddC, and we all know those don't respond very well.

So I think, you know, there are populations where I think we can get a better look at this. But in highly treatment-experienced population, I think the best cuts you can make are T-20 and no-T-20, where you adjust for the really

active drug that's added. And both we and the FDA have done that.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: Yes, just one simple question related to the lipids.

When you measured cholesterol increasing with tipranavir/ritonavir, it looks like you measured total cholesterol. Was specific LDL measured? Was that increased, as well? Because, as you know, as triglycerides go up, your total cholesterol goes up, carried by VLDLs. So I was just wondering if it was an LDL cholesterol..

DR. McCALLISTER: Dr. Corsico again, please.

DR. CORSICO: It was not a direct measure of LDL cholesterol. And that's just, in part, because of the hypertriglyceridemia, which made it more difficult to measure the overall cholesterol. We took the HDL and then had to use that to determine what the LDL was.

DR. GERBER: And the other thing is: are there any data on tipranavir alone? I mean, this

drug has been around forever. I remember it back in the '90s, when Upjohn was working on it.

Does tipranavir alone do anything to lipids? Are there any data that are known about that? Or is this all secondary to ritonavir or a combination?

Obviously, it can't be ritonavir because of the comparator arm, which has ritonavir in there.

DR. CORSICO: In terms of pure tipranavir data, I don't have that data available, or have that data.

We do have a look, though, to see what component ritonavir actually did play in terms of elevating lipids. And if I could show the slide that shows the mean increases in lipids, based on tipranavir dosage in our 1182.52 study, please.

[Slide.]

And what you see in this slide here is the 500/100 dose, the median baseline triglyceride level of 263, with the interquartile range. And then the median maximum increase: 161.

And the 500/200 mg dose, it's 221; and then the median maximum increase is 271.

And then in the 750/200 mg dose, the

median baseline is 223, but the median maximum increase is 196.

Based on this data, we presume that the driving force for a lot of the triglyceride abnormalities is really the move from 100 mg of ritonavir to 200 mg of ritonavir.

I hope that addresses your question.

DR. ENGLUND: Other response that I'd like the FDA to say something about? Oh, Dr. Melisse Baylor?

DR. BAYLOR: Yes, my name's Melisse Baylor, and I reviewed the Phase I studies of health volunteers who received tipranavir. And those Phase I studies included healthy volunteers who received both tipranavir alone, or tipranavir boosted. So there were studies of tipranavir alone.

And I analyzed the patients who started the study with a normal triglyceride level at

baseline. And we had several patients--and I just don't have it in front of me--that had, there were increased triglyceride levels of greater than the upper limit of normal, and Grade 2 increases on tipranavir alone in healthy volunteers with normal baseline.

DR. ENGLUND: Thank you.

DR. McCALLISTER: The studies Dr. Baylor's referring to were conducted in healthy volunteers, and they were just through 11 days of tipranavir monotherapy. And, as she correctly said, there were no patients with Grade 3s or 4s.

DR. ENGLUND: Thank you. Dr. Rodriguez-Torres?

DR. RODRIGUEZ-TORRES: Yes, I have two quick questions on the protocol.

I noticed that the percentage of patients that were co-infected with B and C was low--10 percent in RESIST 1, 19 percent.

These were excluded from the protocol?

DR. McCALLISTER: No, patients with hepatitis B and/or C were permitted. However, all

patients had to be reasonably well controlled; that is, they could only have ALT or AST elevations up to Grade 1.

DR. RODRIGUEZ-TORRES: Still it's lower than what we should expect from this population.

The second question: I notice also that you had availability of expert panel to help investigators select the PI and the optimized background panel.

How many of the sites actually used that help? How many of the investigators used that help?

DR. McCALLISTER: It was a little bit interesting. We had three different experts that were available to any investigator in the world, across both RESIST 1 or 2.

And about 30 percent for RESIST 1--a little bit higher, almost 40 percent for RESIST 2--chose to take advantage of the RESIST expert panel. And we did find, not surprisingly, that when they followed the advice, the response was a little bit better than when they did not.

DR. RODRIGUEZ-TORRES: Okay.

I have another question, but I think it's FDA.

DR. ENGLUND: As long as it's quick. Is it a quick question?

DR. RODRIGUEZ-TORRES: Well, I think it's FDA mostly.

I would be interested to know if the mutations that developed during treatment were divided between the group that used T-20, and the one that didn't use T-20.

DR. JAMES: I'd ask Dr. Naeger to address that question.

DR. NAEGER: For the patients who developed mutations, we didn't group them by the use of T-20. So we didn't look at that.

DR. ENGLUND: Okay. Thank you.

Dr. Wood?

DR. WOOD: Yes, my questions are regarding hepatotoxicity, and whether or not the sponsor has any data out to Week 48, since it seems like during the first 24 weeks, if individuals had a Grade 3 or

Grade 4 they were continued.

And so my first question is: is there any evidence of an increasing risk of hepatotoxicity with continued therapy? Or does the hepatotoxicity pretty much develop within the first 60 days?

The next issue relates to the correlation of virologic efficacy at 48 weeks, and whether or not that is sustained. Given the risk benefits between virologic efficacy, as well as hepatotoxicity, those are my two primary concerns.

DR. McCALLISTER: Let me take the efficacy part of your question, if you don't mind, first.

The FDA hasn't had a chance to fully review our 48-week data from the RESIST studies. And, in fact, we haven't put it together yet in final clinical trial reports for them.

However we do have--I can say that on the basis of this one slide--

[Slide.]

treatment response at Week 24, which we have seen in the tipranavir arms of 41 percent, is sustained in RESIST 1--33 percent of patients; 34

percent of patients in RESIST 2; whereas the comparator arm: 16 percent and 15 percent.

But, again, these data have not been fully reviewed by the FDA.

Regarding your safety question, Dr. Corsico again, please.

DR. CORSICO: We actually have a Kaplan Meier analysis of both our RESIST program, as well as our integrated long-term follow-up study. And I'll show the 17 study first.

[Slide.]

And these are for patients who are receiving tipranavir in the long-term follow-up program. And what you see is this increase rise through Week 48, and then it continues and at this point it appears to be leveling off at around 15 weeks. But there are few data points--few patients at risk. And that's really out at around 90-plus weeks of therapy.

DR. ENGLUND: Dr. DeGruttola?

DR. DeGRUTTOLA: Yes, I have a number of questions about the analysis.

In slide 51, that looked at the COX model for risk of Grade 3 or 4 ALT, AST, were the different predictors--baseline value, CD4 count,

hepatitis--were they included simultaneously in a model, or were they done separately? And if they were looked separately, were they looked at, in some of them, only in the tipranavir arm, or were they all in both arms?

Slide 51.

DR. McCALLISTER: Dr. Corsico?

[Slide.]

DR. CORSICO: Yes, actually, we looked at them separately by treatment, and then we actually put them into the combined model. So there was a comparator model, there was a tipranavir model, and then there was the combined model.

DR. DeGRUTTOLA: So this is the combined model. I see.

Also, I have a question about slide 65: the predictors of antiretroviral response. This is a multiple regression model, and includes the tipranavir score.

Was that score included for all patients, whether they were on tipranavir or not? And, if so, did you look at an interaction with tipranavir? I mean, was the score more predictive among the patients who got tipranavir?

DR. McCALLISTER: Dr. Mayers, please.

[Slide.]

DR. MAYERS: In this model, the score was only for the patients on tipranavir, and the tipranavir is the intercept.

DR. DeGRUTTOLA: I see. But this--does the model include all patients, since it has a tipranavir treatment effect, it must include all patients. So this is the tipranavir score--

DR. MAYERS: No, this is the effect of a regimen containing tipranavir on viral load response at 24 weeks. And we've imputed the intercept, where there's no active drugs. There's a tipranavir score of zero. There's a--and it's the tipranavir/ritonavir effect.

DR. DeGRUTTOLA: I guess I'm still a little confused.

Does this analysis include all patients? I assume it does, since there is a tipranavir effect on the first line.

DR. MAYERS: No, it does not.

DR. DeGRUTTOLA: So-o-o--how do you--

DR. MAYERS: If you set the active drugs to zero, and you set T-20 to zero, and you set the tipranavir score to zero, the intercept is what we're imputing the tipranavir effect to be.

DR. DeGRUTTOLA: I see. So this is an analysis only of patients receiving tipranavir.

DR. MAYERS: Yes.

DR. DeGRUTTOLA: Okay.

I had a question about the--I noticed there were 34.2 percent of patients that were receiving tipranavir in both RESIST studies that had viral load below 400, and 41 percent that had the 1-log drop. In the 48-week data that we just saw it looked like there was this response rate of about 34 percent.

So I had a question about the patients--the 7 or so percent that had greater than

a 1-log drop, but did not go below 400. I'm curious if those have been included in any of the analyses of the resistance mutations that developed on study. The FDA mentioned in their analysis that they looked at mutations developing among failures. So this is a question about the patients who had the greater than 1-log drop but didn't go below 400.

And I also had a question: if anyone had looked at durability of the effect in those patients.

DR. McCALLISTER: So your question is: those that had a greater than 1-log drop but didn't go below 400, were they included in the resistance analyses that Dr. Mayers showed?

DR. DeGRUTTOLA: Right. And is there any information about development of resistance in just those patients?

DR. MAYERS: No, we don't have any analysis of that.

Basically, the samples that we submitted and the FDA analyzed were either patients who had

no response from baseline to initiation of therapy, or patients who'd had a response and then had a rebound above. So that patients who had a response but still had detectible viremia, we haven't analyzed at this point in time.

DR. DeGRUTTOLA: Okay.

And one quick final question: for the question that Dr. Haubrich raised about the CD4 analyses, was that an analysis where the last value was carried forward? Or was that an analysis where, after the patient dropped out of the study they just weren't included any further?

DR. MAYERS: That was a last observation carried forward analysis.

DR. DeGRUTTOLA: Thank you.

DR. ENGLUND: Dr. Sherman.

DR. SHERMAN: Thank you.

Several questions--I'll start with a GI-related question: interaction with antacids, is this a binding reaction, or is this a lack of acid in the stomach issue?

DR. McCALLISTER: I'd like our colleague

DR. Kashuga to help with that. However the data that we showed in that study indicated that when tipranavir was co-administered with antacid, there was approximately a 25 percent reduction in tipranavir levels.

DR. SHERMAN: Yes, that could occur either way, though--binding or low acid. Because if it's low acid, it raises two issues: use of PPIs and H2 blockers in patients on an ongoing basis. And in patients with late-stage HIV, there is frequently a failure of gastric acid secretion.

DR. McCALLISTER: Right. We didn't specifically analysis that. I can maybe indirectly get at your question by showing you some data from our RESIST studies, where we looked at patients who had--if I can bring this slide up--yes--

[Slide.]

--tipranavir trough concentrations in the presence of proton-pump inhibitors, on the left-hand side you see the large number of patients--506--who did not use a proton-pump inhibitor, and the median tipranavir concentration

here of 33 micromolar. The patients who did use a proton-pump inhibitor, 39.3. But the end was only 44. That's as close as I think I can get.

DR. SHERMAN: Okay.

Some other questions related to the analysis of the hepatotoxicity data: you've shown by strata of Grade 3, 4 ALT abnormalities. Do you have this broken down among those with abnormalities, for mean or median ALT levels over time--which would permit us to include those with lower levels of abnormalities?

DR. CORSICO: Those analyses we do not have.

DR. SHERMAN: Do not have. Okay.

And when you said there was "resolution of LFTs" in patients that were stopped, who had Grade 3, 4, you meant resolution back to a lower grade, not necessarily resolution to normal.

DR. CORSICO: Well--or their baseline.

DR. SHERMAN: Or their baseline.

Were there liver biopsies performed on any subject during periods of flare?

DR. CORSICO: We have a case in--not in the RESIST program, but there was a patient who actually did have a liver biopsy in the setting of

a flare. And that patient actually was, on biopsy, found to have what the investigator reported as a drug-induced hepatitis.

But the liver biopsy data that we had would only be in the setting of a serious adverse event that was reported to the company.

DR. SHERMAN: And is that comparable to what was seen in pre-clinical animal studies, with liver toxicity?

DR. CORSICO: For that, actually, I'd like to call up our pre-clinical toxicity expert, Ms. Dursema.

MS. DURSEMA: Hi, I'm Holly Dursema. I'm the toxicologist that has been handling tipranavir since we end-licensed it from PNU in 2000.

Regarding animal toxicity studies, we did some minimal toxicity. Most of our studies were conducted in rats and dogs. We saw very little liver toxicity there. Our predominant liver

finding was hepatacellular hypertrophy--which is a known effect of an enzyme inducer such as tipranavir.

We did see some liver toxicity in mouse studies, where we saw elevations in ALT and AST. We saw some single-cell necrosis. We did have an expert on pre-clinical hepatotoxicity look at these studies, and his evaluation was such that he felt that it wouldn't be necessarily a serious indicator of serious liver toxicity with a risk for humans.

DR. ENGLUND: Dr. Morse?

DR. MORSE: This may have been said and I just missed it, but for both groups: there were some separated discussions about inhibitory quotient. And I think I heard mention of a target, initially, of about--or the concentrations at the selected dose would achieve around 25. And then in the FDA analysis, I think I was hearing something along 100 was discriminating.

So the question is: is there actually data just showing a spread of the IQs achieved and the response? And, using the FDA analysis, how many

people would actually have a suboptimal IQ at the dose that is being put forward?

DR. McCALLISTER: My colleague Dr. Mayers, please.

DR. MAYERS: If we could have slide 39, please.

[Slide.]

This shows the two-week data in our functional monotherapy study, in which tipranavir--we have pure tipranavir effect.

And, as you can see, for at least antiviral activity, we saw a threshold of approximately 30 in these patients--we have on the y-axis is the viral load reduction; the x-axis is the inhibitory quotient.

If we go to the next slide--

[Slide.]

--this shows the group data, and shows that, basically, above 30 was associated with a 1-log response without a significant increase above 30 for two-week responses.

Now if I could have the next slide.

[Slide.]

This shows the 24-week viral load response by inhibitory quotient in patients not using T-20.

And so, again, you see when you get above 30 you start to get responses, but there's a fairly large spread in the data.

We then have the same data on the next slide--

[Slide.]

--using T-20. And again we see that when you get above 30 you start to see a response, but there's a very large spread out at 24 weeks with inhibitory quotient.

DR. ENGLUND: I think the FDA wanted to say something here, too.

Dr. Jenny Zheng.

DR. ZHENG: Actually, our analysis demonstrates there is a relationship. With regard to what the target is going to be, I think depends on your expert judgment. Because if you want to reach 60 percent of response rate with T-20, this is going to be--if it is 60 percent, this is going