to be the target. It's going to be.

If you want to reach the 30 percent of response rate, you can predict--you can calculate the target.

So, the analysis is not about the efficacy of tipranavir itself. Because as compared with comparator here, at this IQ ratio, tipranavir shows advantage over the control arm.

It's about "can we do it better for the patients?" For example, patients here, they have low IQ, but they're still better than comparator. But if you can increase those to increase the inhibitory quotient, you can do better. That's what our analysis showed.

So, again, what target is going to be depends what response you expect.

DR. ENGLUND: Dr. Morse, does that answer your question?

DR. MORSE: I think my coffee ran out, there. Sorry. Go ahead.

I can't tell if they were going to present something up there, or--

DR. NAEGER: Yes, we have an additional table looking at the response by IQ, which might make it easier to see.

Back up--36.

DR. MORSE: While you're getting that, I could just clarify my question.

I think I'm thinking more of the way lopinavir data was presented, with change in viral load as different IQs were reached. Maybe that's just--I'm not sure I saw that in either of those.

DR. NAEGER: We looked at--

[Slide.]

--this shows proportion of responders, and this looks at the spread by the median IQ of 76--this is for the RESIST 1 and 2 trials, and then also by quartiles.

And you can see those less than 76, the response rate was 29 percent; greater than 76, 64 percent. And then by each of the quartiles, you can see the increase.

Does that help?

We don't have it by change from baseline.

DR. MORSE: Yes.

DR. ENGLUND: Okay. Edmund, did--does someone else have a question about this IQ? Because I'd like to relate to this here.

Okay. Well, you already got to ask a question.

DR. CAPPARELLI: And, actually, mine has to do a little bit with a procedural question.

Half the IQ obviously is the trough concentration. And as what I've heard--and I haven't heard it explicitly stated, but I think it was mentioned by the FDA presentation--that there was a range of times at which things were collected that was acceptable for a C min, from nine to 15 hours. Is that correct? Because that's a full half-life. So there's an order of magnitude range.

And then the other related question is: was this only done once? And, you know, from that standpoint, if it was done more than once it would be nice to have some feel for the intra-patient versus inter-patient variability.

What's been expressed looks like it's sort

of a mix of both. But to understand those, I think, has implications on our assessment of TDN.

DR. ZHENG: For the Phase III study analysis we used trough concentration, actually, from Phase III study trough concentration has been collected. So that's the mean after three.

They also did analysis for Phase II study. In that analysis, which is shown as the green line here, they didn't use "observed" concentration. They used predicted from [XXX sounds like POPPY PEE] analysis.

So it means that for this analysis, the time factor actually has been controlled. But not for Phase III.

For Phase III we tried to limit the time effect. That's why we limited sample collection time from 10 hours to 12 hours--I'm sorry, 10 hours to 14 hours, because trough concentration is the time, 12 hours after the dose. So we know that sampling time would have introduced error into this measure. That's why, for the trough concentration we used the penetration window--time window, which

is 10 hours to 14 hours.

DR. CAPPARELLI: And the intra-patient variability?

DR. ZHENG: Intra-patient variability is 51 percent from--inter-patient variability is 51 percent. Intra--actually, is 36 percent. That's based on the assessment from Phase II study.

In the Phase II study, samples were collected at Day 7 and Day 14. Using that data, we estimated the intra-subject variability.

DR. CAPPARELLI: But I think the Phase III study, it may be different--the intra-patient variability may be much different.

DR. ZHENG: Yes. I think in order to have a better estimate on intra-subject variability, we think Phase II data is more reliable because samples were collected at Day 7 and Day 14, it's more controlled.

For the Phase III study, the samples were collected at Week 2, Week 4 and Week 16. So we can see the spread of that.

So any difference could be intra-subject

variability. It could be the effect of the other components.

So, to purely calculate, to estimate intra-subject variability, we believe Phase II data is more reliable.

DR. ENGLUND: Thank you.

Dr. Hall, did you raise your hand? Oh. Well, then would you like to ask a question?

DR. HALL: No.

DR. ENGLUND: Okay.

Dr. Miller?

DR. MILLER: I was going to ask about information on non-B subtypes, especially in relation to the emerging mutations.

The question regarding information on non-B subtypes, especially with relation to the emerging mutations that come up under treatment.

DR. McCALLISTER: Dr. Mayers, please.

DR. MAYERS: Can I have "Resistance" slide 44, please.

[Slide.]

We've looked at a panel of non-B subtypes

against tipranavir, and I think the most interesting one probably is the clade G, where there are three natural polymorphisms that are tipranavir-associated mutations. And at this point we don't see any decrease in susceptibility. This is mainly in Portugal, and we've just opening the Expanded Access program in Portugal, so I don't have any emerging data. But we are going to work with Ricardo to look at is there a different path to resistant with G's for example. So it's our intention to work with outside investigators.

At this point, we have very few non-clade B's in our pivotal trial program. Even in Europe, most of the patients who are highly treatment-experienced are clade B. So we think we'll get a much better handle on this in our naive patient program where we have a much more diverse population and have a much higher prevalence of non clade B. So we're going to follow that.

But this way, almost all of our data is based on clade B pathway to emergence.

DR. ENGLUND: Thank you.

Dr. Maldarelli?

DR. MALDARELLI: Yes, I was wondering if you might clarify two points, first, regarding

resistance.

With the phenotyping assay, was that done in house, or as a commercial assay? There have been changes in cutoffs and so forth with respect to lopinavir and ritonavir over the last four or five years. How were those handled with respect to the trial? And sort of the same question in terms of genotyping, how that may have changed over the four years.

The other part of that question regards: you mentioned position 48 as a point that it appeared to be something that made the virus more sensitive.

That's the first set of clarifications.

The second has to do with the conduct of the trial itself. I was wondering if you might expand on the protocol violations occurring in 50 percent of the patients; whether that was something that occurred up front, occurred consistently

throughout the trial at single sites?

Secondly, with regard to protocol conduct, the list of fatal events--at least the ones listed in our book--in terms of cause of death was not attributed in all cases, or at least not reported. And the fact that you had an exclusion criteria for patients who were not expected to live for, I guess, a year, and a number of those deaths had occurred at least within a week to six weeks of entry.

DR. McCALLISTER: So, the three parts of the question--I think for the phenotypic information, we'll have Dr. Mayers first, please

DR. MAYERS: I'd like to initially have slide 34 from "Resistance."

[Slide.]

Basically, almost all the samples we ran for our pivotal trial program--and our analyses were done by the VIRCO assay. But we have a set of isolates that we've run with both VIRCO and Viro Logic on the same sample.

And what I can tell you is basically: they

are linear and they do give the same break points if you do an IQ analysis or a resistance analysis. So it's our opinion at this point that the breaks that you saw given were VIRCO breaks, but we believe that we would get the same answer using ViroLogic for the same data set. Because we did look at one trial that way and found the same break points.

The 48 mutation--I'd like to go to slide 51, actually.

[Slide.]

Interestingly enough, there are a number of positions which are associated with decreased resistance, or increased susceptibility to tipranavir. Looking at position 30, 88 and 50--so the 30 and the 50V, and the 88D all actually produce viruses that are more susceptible to tipranavir than you would have thought. So they would actually be negative if we had a weighted score.

48 doesn't show up in the phenotypic susceptibility, but we also have seen that 48 is

associated with better virologic responses if it's present than if it's not present.

So we've seen the same observation that the FDA has made.

Does that answer the resistance part of the questions?

DR. MALDARELLI: And in terms of your scoring, the rules sort of evolved over the course of the trial. Did you use rules at the end? Rules at the beginning? Or did you evolve, as well?

DR. MAYERS: The rules evolved, but the major rule change actually occurred right at the beginning of the study before patients enrolled. And what happened was, we showed our 52 data at the Resistance meeting, and showed the responses to lopinavir and the susceptibilities. And actually we, because of our own Phase II program, ended up redefining with Bayer what the phenotypic susceptibility was to lopinavir, which is why it went from 27 percent of the patients being scored as resistant, to a very high percentage being scored resistant.

So, unfortunately, we drove--fortunately or unfortunately--we drove a major change in the interpretation right before we opened our Phase III

program. But after that, there's only been modest changes. We have allowed those to continue be cause it did seem appropriate to give the docs the de-tuned versions of the algorithms.

And, as you know, for VIRCO, with their virtual phenotype, it changes--every night, I guess.

DR. ENGLUND: Dr. Washburn?

DR. MALDARELLI: Actually--

DR. McCALLISTER: There were a couple other pieces to his question.

DR. ENGLUND: Oh, that's right. Okay.

DR. McCALLISTER: Is that okay?

DR. ENGLUND: Yes.

DR. McCALLISTER: Protocol violations: the protocol violations in the two RESIST studies were larger than we had anticipated early on. However, what we did was a sensitivity analysis that actually would take those that were clinically

relevant and remove them from the data set. And even after removing that large number of protocol violations, as you saw, the treatment response was still significantly superior in the tipranavir arms.

And they occurred--I think, in direct answer to your question--at multiple time points in the study, in terms of screening violations, where they might have checked the wrong box on the eligibility criteria; or patients who made changes in the whether or not they were going to use T-20.

There was no particular pattern to it.

DR. MALDARELLI: It seemed like there were a number of violations in terms of entry criteria for their genotypic analysis, and yet a number--or at least 30 percent--consulted the expert.

Were any of those violations--did those violations occur in those interactions?

DR. McCALLISTER: So you're asking: of the patients who had protocol violations in terms of the baseline resistance status, what were--I'm sorry, I didn't follow the last part.

DR. MALDARELLI: Did they consult the experts? So, in other words, could the experts have excluded those patients for you--or did that

happen?

DR. McCALLISTER: Yes--we didn't look at it in that way.

We required any investigator to consult the expert if they wished to choose a PI that was not considered the most susceptible on the report. We also offered them to consult one of our experts for any other reason.

But your specific question, we have not looked at.

The third part of your question had to do with the fatal events. And, as I mentioned earlier, we did not apply any objective criterion to keep people out of the trial. It was all subjectively left up to the individual investigators.

And, yes, there were some patients that died early on. So those were potentially mis-categorized.

DR. JAMES: I think another part of the mortality question--that neither of us presented--was that there were a number of subjects who died in the pre-treatment period. So they were screened and enrolled, however never made it to treatment and died beforehand.

So this was a very sick population. And it looks like maybe a very desperate population, because the rule of living for at least 12 months seems to have been ignored in some of these cases.

I think--I'm forgetting. There was another part to the mortality question that I wanted to address--oh, the causes of death. You said that there were diagnoses--

DR. MALDARELLI: There were several that were not reported/

DR. JAMES: --diagnoses that were "unknown." And that's how the reports came in to the FDA. "Subject found dead at home. No further information available."

So where there was no further information, that's all we had.

DR. McCALLISTER: Certainly we've made aggressive efforts to follow up on those patients as much as possible. But in some cases the investigator had no ability to get additional helpful data for us.

DR. ENGLUND: Thank you.

I think our last question before we're going to break--but I just want to urge you--write it down. Don't forget it. We have some time

afterwards for questions, but we're going to have to take a break.

So--Dr. Washburn.

DR. WASHBURN: I actually wanted to go back to follow up on the first question which was asked by Dr. Grant. I'm still struggling with the issue of compliance, given this study design.

It's somewhat reassuring to know that the pill counts were equivalent in both arms. I think we heard about 95 percent compliance. But, unfortunately, that still leaves open the possibility that in one arm the study subjects were flushing their pills, and in the other arm they

were taking their pills.

Whatever they did, they did it before they went for their follow-up visit.

In the tipranavir arm, we have the reassurance of knowing that resistance mutations emerged on therapy--which I take as kind of a surrogate marker of compliance.

Do we have that kind of information in the control arm?

DR. McCALLISTER: What I can tell you is: in order to leave the comparator arm and go to the .17 study to receive tipranavir after the Week 8 escape, we did consider the possibility of a patient intentionally sabotaging their own treatment, and we did require not only the confirmed virologic failure, but we required drug levels. Those were measured, verified, and then they were permitted to go--if they were there.

DR. WASHBURN: Thank you.

DR. ENGLUND: Dr. Bhore?

DR. BHORE: Yes--we were also concerned about the compliance issue, especially in the

comparator arm. And we don't know if pill-count data is really that reliable.

So, therefore we looked at data on the drug concentration in the patients for those particular drugs that they were assigned to. And we did a separate analysis, which was not shown in our presentation.

But what we did was we looked at patients who did not--had undetectable blood concentrations at Week 2 and at Week 4, and their viral load was going up. So we regarded that as a suspect case of patient's intentionally not taking their medication so they can leave the trial and, you know, fail early on.

And with that analysis, we found that the treatment effect was about 10 percent--which is the treatment difference--with a lower confidence bound of 1 percent.

DR. CAPPARELLI: Just one question on that--how frequently did you encounter the levels being low at multiple visits? What portion of patients was that?

VOICE: [Off mike.] [Inaudible.]

DR. ENGLUND: Excuse me. You've got to identify yourself--or just repeat it.

DR. BHORE: That is Dr. Tom Hammerstrom, who helped us out with that analysis. He's saying it's 100 out of 500.

Only on the control arm, because we were concerned about only the control arm not taking their medication.

DR. CAPPARELLI: So it's 20 percent.

DR. ENGLUND: Okay.

Well, don't forget your questions, Committee people.

I have a couple of announcements.

We're going to reconvene at 1:25 because we really want to get through all our questions today.

I need to have a couple of announcements: the registered open public hearing participants need to register at the registration desk if they have not done so. This will be conducted after lunch.

For the Committee members, we will be escorted to the restaurant because if you don't know the way, you will end up in the garbage dump.

[Laughter.]

You have to go outside the hotel, and I can guarantee you that an escort might be helpful.

For those of you not on the Committee, there are lunch places across the parking lot also.

So, with that, we will be dismissed until 1:25.

Thank you.

[Off the record.]

DR. ENGLUND: I'd like to call the afternoon session to order.

And we're going to start with some--I've just lost my person who's doing it. Anuja?

We're going to start with a brief awards presentation, to be followed by the Open Public Hearing.

And Dr. Birnkrant is going to announce these awards.

## Awards Presentation

DR. BIRNKRANT: Good afternoon, and welcome back.

It is my pleasure to present Drs. DeGruttola, Englund and Wood with these service awards, as members of the Antiviral Drugs Advisory Committee.

All three experts have served since 2001, and have been involved in meetings ranging from a drug for the common cold, to therapies for

hepatitis B, to clinical trial design issues for topical microbicides, and the current meeting today.

We want to thank them publicly for their contributions to the FDA and the public health of our citizens.

All three will receive plaques and a letter from our Acting Commissioner.

Dr. DeGruttola--if you would come up here--from the Harvard School of Public Health, we would like to thank you for your time and effort and your significant input to the FDA.

[Applause.]

DR. DeGRUTTOLA: Thank you.

DR. BIRNKRANT: Dr. Wood, from the National Cancer Institute--we would also like to thank you for your dedication to our Committee and for providing valuable input, not only related to pediatric drug development, but to antiviral drug development in general. Thank you very much.

[Applause.]

DR. WOOD: Thank you.

DR. BIRNKRANT: And Dr. Englund, from the University of Washington, for serving on the Committee and participating in 11 meetings,

including chairing three meetings--and, again, providing meaningful contributions to antiviral drug development. Thank you very much.

[Applause.]

DR. ENGLUND: Thank you.

And I was told they would take it away from me if we don't finish on time.

[Laughter.]

Open Public Hearing

DR. ENGLUND: So--with that, I would like

to open this meeting to the Open Public Hearing, and I first have to read aloud a short paragraph, prior to opening this to the public forum.

It states:

"Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

"For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product and, if known, the direct competitors. For example, this financial information may include the sponsor's payment of travel, lodging or other expenses in connection with your attendance at the meeting.

"Likewise, the FDA encourages you, at the beginning of your statement, to advise the

Committee if you do not have any such financial relationships.

"If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking."

And, with that, we'd like to have our first speaker--our only speaker? Our only speaker--Rob Camp from the Treatment Action Group, who will present a summary statement.

DR. CAMP: Hi, my name is Rob Camp, and I work at the Treatment Action Group in New York City. Treatment Action Group is a non-profit AIDS advocacy organization, and we have no conflicts of interest. We receive approximately one-third of our funding from private donations, one-third from foundations, and one-third from a various array of the pharmaceutical industry.

Our latest annual report can be seen at www.treatmentactiongroup.org if there are any other questions.

Also I'm going to talk about a paper that I sent to the FDA, who was kind enough to

distribute it to the whole Committee here who's here today. The full report is also available at the same website: www.treatmentactiongroup.org, if anyone would like to read the whole thing. There's a short version outside.

The points I want to make have been signed onto by a group of, right now, about 10 organizations around the United States--it's not only Treatment Action Group. Ten organizations from Washington, Texas, Chicago--may places around the U.S.--as well as a national coalition of AIDS activities called the Drug Development Committee.

Okay--getting right down to it--TAG recommends--and all of the other organizations--recommend that the FDA approve the Boehringer Ingelheim application for accelerated approval tipranavir/ritonavir to treat advanced HIV infection in combination with other active antiretroviral agents in treatment-experienced adults with evidence of HIV replication despite ongoing antiretroviral therapy.

I would just like to make a couple of

specific comments.

This morning we noticed that we heard a lot from the sponsor, as well as the FDA, that the resistance profile is fairly difficult and complicated, and it needs to be clearly stated on the label, as well as all patient information, as clear as possible, for everyone to understand, how and when it can best work with the mutations that a patient may have.

A side question I had from this morning is: did those docs who took advantage of the expert advice, did their patients do better than those who didn't use that advice?

Anyway--we also heard this morning that a second active agent needs to be included in the regimen with the tipranavir/ritonavir in this patient population. And we heard mostly about T-20.

It's too bad that we're not here today to approve the combination of tipranavir/ritonavir/T-20, because then I'd give two really big thumbs-up. As it is, it's just sort

of--[laughs]--no.

But the problem with T-20, of course, is the problem it's always had: its cost and its administration. So even though there is a good second agent out there, it's not a perfect second agent.

Tipranavir/ritonavir has a challenging safety and tolerability profile. And in order to "do no harm," clinical management needs to be meticulously addressed: addressed by the Committee here today, by the FDA, and eventually by the sponsor when the drug gets out there on the market.

We strongly suggest that the patient information for the two drugs, tipranavir and ritonavir, be designed as one entity so the patient understands what their taking. They're taking 400 mg of ritonavir. It's not a low-dose boosted ritonavir. It's actually twice as high as any other ritonavir-boosted PI that's out there now. It's four times more than the ritonavir you'd take with atazanavir.

So it's really important that people

understand that they're taking two drugs, and how do these two drugs--how do you take those two drugs together.

The studies we'd like to see before full approval, within the next year, are dosing studies. I think the IQ idea is very, very interesting. And tipranavir/ritonavir, with alternate ritonavir dosing, as well, could be investigated in various populations.

PK studies, interaction studies need to be done with new and upcoming ARVs, and concomitant medications like PPIs, sildenafil, covermezapine, etcetera.

What I was a little surprised about is that even the studies that have been done, there are no recommendations. When you have abacavir, with a 40 percent decline in $C_{max}$, there's no recommendation? Why are these studies being done if there is an effect seen and no recommendation comes out of it?

We're glad that pediatric studies are under way. Liver safety studies--guidelines need

to be developed in order to best define the population that can most safely use this drug.

Long-term safety studies; complete and rigorous safety data collection and reporting, both within trials and in the real world need to take place through a strong pharmacovigilance.

The recent developments in the Drug Safety Division of FDA, as well as the recent FDA Safety Act submitted by Senators Dodd and Grassley need to be paid close attention to. Ideas like sentinel sites, more effective signaling, FDA having more authority over post-approval studies and marketing, civil penalties, as well as more accurate warning and safety systems are all overdue and needed in HIV.

Eleven percent total of women in these studies give a confidence signal of what can be expected in women. I got the feeling this morning that the FDA is uncomfortable with that. And if that's the case, I demand from the FDA that they demand of companies to do something about that.

We're happy--we're very happy--to see

that--again, this morning I felt that FDA wasn't thrilled with the eight-week OBR data in the CPI arm. We're happy to see that because it's basically a virtual placebo arm. So I think eight weeks is more than enough for that.

But the issue, of course is: well, how do we get longer-term data in a salvage population? I have a little phrase--I call it MEAT--which is multi-experimental agent trial--which is basically where you use tipranavir/ritonavir with many other experimental agents in the same trial, with an experimental NNRTI, versus an experimental injury inhibitor, versus an experimental CXER4 inhibitor. And we'd be here today talking about many different things, rather than just "remember to use it with T-20, if you can."

Finally, I think that in this authoritarian day and age, FDA needs to be Cruella De Vil with these 101 Dalmatians--in the sense that you're controlling all these dogs, and how do you do that? How do you all walk down the street together?

And I think that we find it a little absurd that we, the community, are saying yes to accelerated approval for a drug that shows 35

percent success rates, in a field that already has 20 other drugs out there.

We'd like to do better, and we think we can do that through multi-experimental agent trials.

Thanks a lot, both to the FDA, the Committee and to the sponsor of this drug.

Thank you.

[Applause.]

DR. ENGLUND: Thank you very much.

Committee Discussion/Questions to the Committee

DR. ENGLUND: With this--I'd like to have--there's a few people that didn't get to ask their questions before lunch. We're going to have, actually, a response from the FDA to specific question, and a response to the company.

And then we're going to go directly to the Questions, because I'm hopeful that by focusing on the individual questions we'll be able to have time

for discussion. There are some important discussion points that we want to have left.

So, if people remember what questions they had--Dr. Wood was first on my lift.

DR. WOOD: My question was for the sponsor, as well as for the FDA and the sponsor.

The first issue was that, in terms of the drug interaction studies, we saw reduction in all the PIs that were tested--saquinavir, amprenavir--as well as lopinavir. There was a limited number of individuals on the RESIST 1 and RESIST 2 study--I think it was about 21--but I was wondering whether or not the company had any data regarding drug interactions with tipranavir and indinavir, based on that on-study population.

The second issue goes to the fact that we clearly know that there's major inhibition of the CYP 3A enzymes, but we also know that there's likely to be involvement with the CYP 2D6, as well as the CYP 2C9.

And I would just like either the FDA or the pharmaceutical sponsor to comment on classes of

drugs that are likely to be involved, in terms of metabolism by these cytochrome P450 enzymes.

DR. McCALLISTER: The answer to your first question, about in the RESIST studies-- there were a very limited number who took a dual-boosted PI, and that was considered a protocol violation. We don't have specific data on the interaction between tipranavir and indinavir from that study.

Your second question, at least for the BI part, I'd like to call on my clinical PK colleague, Dr. Tom McGregor. We do have some data from our RESIST studies, looking at other enzyme pathways.

DR. McGREGOR: Good afternoon. I'm Tom McGregor, from R&D.

And if I could have the first slide.

[Slide.]

In the laboratory an in vitro assessment of tipranavir to inhibit the cytochrome P450 pathways, it was noticed that given a C max value of 95 micromolar, any CYP enzyme that would be below 95 would have the potential for an interaction. So this is 1A2, 2C9, 2C19, 2D6, and 3A4. The rank

order of these would be: 2C9, 3A4, 2C19, 2D6 and 1A2.

If I could now have slide 87.

[Slide.]

The way we developed our drug interaction program for accelerated approval was to worry first about the particular drugs that are used in practice in the treatment of AIDS, and we see that the majority of them are, as expected, CYP 3A4 drugs. And so this was the pathway that we looked at the most.

Second of all, we looked at the P-gp pathway because we did a study with loperamide. We were worried that if ritonavir inhibited this pathway, we wanted to make sure that there was no interaction at the blood-brain barrier, such as there is with quinadine and loperamide. So this was the next area.

We are not forgetting these other areas. We did look--we are planning to do studies to look at them. But, if you think about it, the 2C9, which was the one with the biggest inhibitor,

primarily the drugs that were used in the .12 study were, in fact, the COX-2 inhibitors and ibuprofen. The other ones would have a greater impact on 3A4.

So, if I could have slide 83--

[Slide.]

--this is what we plan on doing, as far as the next step in in vitro metabolism, and that is to look at induction of each of these, along with PCR.

And if I could have the slide of proposed in vivo studies--

[Slide.]

--this is the studies that we plan to do in pharmacokinetics.

The first one, that is in the planning stages right now, is a CYP/P-gp cocktail study. Second of all, we are looking at drugs that are, in fact, primarily in those pathways to look at--we have recently completed a methadone study.

So we are continuing to do drug interaction studies. We do feel that it's an important series of pathways, but for accelerated

approval, it was important to do those drug interaction studies that were necessary to get us into the program and find out that the drug works.

I hope that answers your question.

DR. ENGLUND: Dr. Haubrich--you had a question before the break?

DR. HAUBRICH: I'll let Dr. Kumar go. I was actually just stretching. But I do. I'll come up with it.

[Laughter.]

DR. KUMAR: Dr. Englund, can I go?

I've got three safety issues that I would like to ask Dr. Corsico, please?

The first thing again--and I don't want to harp on this, but I'd like to feel like I understand the data.

Regarding the efficacy of lipid-lowering agents in patients that had emergent Grade 3, Grade 4--my question is: did you do anything like a Framingham Risk-Reduction from the beginning of the protocol, at Week 24, or at Week 48, that could help answer that?

DR. CORSICO: That analysis has not been done yet. Actually, we are under discussion on how to actually do that, and we'll be working on

putting that model together so that we can actually have that data.

DR. KUMAR: Very good. Thank you.

My second issue is about rash. In patients that had rash, did they have any--and I'm not sure whether I saw that in the FDA or in your written material--that they had arthralgias with that.

But along with that, did they have anything else? Did they have fever? Did they have increased liver enzyme? And did anybody develop Stevens-Johnson?

DR. CORSICO: If I could, I'll take the third part of your question first.

The rashes that were seen during the development program were non-serious, self-limited rashes typically--macular, papular. No one developed SJS or TEN. There were no deaths due to rash.

With respect to what was seen, particular in the 1182.22 study, where healthy women were receiving ethinyl estradiol plus tipranavir, we had 58 percent of those women develop rash, and actually we discontinued the study.

We actually called in a dermatologist and

called in a rheumatologist because we were concerned about systemic symptoms. And I think--as the FDA has pointed out--there were some women who had overlapping syndrome where they had arthralgias.

Review by the rheumatologist felt that this was not as consistent with a systemic syndrome, because, one, we drew ASO/ESR titres, and while they were mildly elevated, we had no comparator data to compare it with, and it was only a mild elevation.

The urinalyses that were done on these patients showed no evidence of cast formation, and none of the patients developed fever or lymphadenopathy.

Concerned about this issue, though, we did

look at our patients with and without rash to see whether or not we saw any changes in liver function tests.

And if I could have the slide that shows that analysis--

[Slide.]

--what you see here are our HIV-positive patients with skin rash, no skin rash; HIV-negative patients, skin rash, no skin rash; and then Grade 1, 2, 3 and 4 LFTs. And you can see there really is no trend in the patients with skin rash with respect to liver function abnormalities.

Hopefully that addresses your question.

DR. KUMAR: And in your RESIST trials, the percentage of patients who had rash, were they continued on the medications, and did the rash go away? Or did you have to stop the medication?

DR. CORSICO: There were actually a total of nine patients through the September 30th cut that had rash and had to discontinue. Five of those patients received tipranavir, and four of those patients received comparator.

DR. KUMAR: And do you have any data on any patient who had a re-challenge--had a rash, stopped, and then re-took the medication?

DR. CORSICO: We don't. I should tell you, in that data set there were two serious adverse events: one on the comparator arm, and one on the tipranavir-treated patient. But none of those patients developed desquamation or any moist lesions. And in the serious adverse event cases, they discontinued the medication and were not re-challenged.

DR. KUMAR: And within how many days did the rash come on?

DR. CORSICO: It actually depends on which subset you look at. And, actually, there's an interesting difference with respect to how the women who were treated with ethinyl estradiol reacted, versus the other HIV-negative women, versus our HIV-positive women.

If I could have that next slide, please.

[Slide.]

What you see here is this is the trial

where the women received ethinyl estradiol. You see that the time to onset was approximately 10.5 days. In the other HIV-negative studies, the time to onset was 4.9 days. And in our HIV-positive trial--and that was our 1182.52 dose-finding study--you see the time to onset, the mean, was 87.5 days.

The duration of rash, you can as well, differs among the three groups. It's 13.5 in the HIV-positive treated patients, versus 6.7 and 8.8 in our HIV-negative treated patients.

DR. KUMAR: Can I ask my final question, Dr. Englund?

Can you say anything regarding tipranavir and the developing fetus? I tried to look, and I didn't see any information on that.

Do you have any information on that?

DR. CORSICO: Certainly. We actually have seven women who were exposed to tipranavir during the course of pregnancy. And this next slide summarizes those seven cases.

[Slide.]

Six of the women actually had their exposure during the first trimester, and one had during the third trimester. Four of those women

went on to deliver healthy babies, two of which we've been able to confirm, as of now, that are HIV-negative. The other two--although we've doggedly tried to find out what the status of the status of the child was, we still do not have that data available.

There were three women that had either elective termination or spontaneous abortion.

In the one with the spontaneous abortion, the fetus was determined to be small for gestational age, and there was evidence of oligohydramnios--something that has been see in other women, HIV-infected, who have been treated with antiretroviral therapy.

We certainly can't draw any definitive conclusions. However, the company is committed to further understanding this, and we will be putting tipranavir into the antiretroviral pregnancy registry, just as we have with our other product.

DR. KUMAR: Thank you.

DR. ENGLUND: Thank you.

Dr. Haubrich?

DR. HAUBRICH: Just a comment, follow-up--oh, sorry.

DR. BAYLOR: Oh, I'm sorry.

DR. HAUBRICH: Go ahead.

DR. BAYLOR: I'm Melisse Baylor, and I was going to comment a little bit more on our analysis of rash from the healthy volunteers, because you had questions.

And it's interesting, because as the folks from the applicant were saying, that there were no increases in ALT, and there were no desquamations or things like that suggestive of Stevens-Johnson.

But what we did see in healthy volunteers who developed a rash was associated symptoms. We saw--and that's outside of study 22, with the birth control study. So we saw women who developed--two women complained of throat-tightening and swelling and itching at the same time they had a rash.

We had another two women with joint

symptoms. We had a man that had a swollen posterior tongue.

So there are--although it's not Stevens-Johnson, some of the people with rash did have symptoms that were suggestive of more hypersensitivity. But it was varied, and it was rare.

You know, the other kind of unusual thing for us, I think, is we did see in HIV-positive and HIV-negative patients photosensitivity reactions.

DR. HAUBRICH: So, just to follow up on the rash question: looking at the logistic regression analysis that was presented on slide 48, if I'm understanding the analysis here correctly, it looks like the odds of developing rash were actually higher in those with lower CD4 cell count. Yet there seems to be this disparity that there was a higher rash rate in HIV-uninfected people.

Could you comment on that? And then I have one other question unrelated to rash.

DR. CORSICO: Actually you raise an interesting point, because in the RESIST data set,

it's clearly the "less than 50" compared to "greater than 200" that have the increased risk.

At this point in time we are trying to understand this, but we don't really have an answer, in terms of how the HIV-negative patients responded, versus what we're seeing in our RESIST program.

DR. HAUBRICH: And then I guess this next question is probably for Doug Mayers.

In the calculation of IQ it's difficult for me to understand that's .1 percent free has an IQ of over 100.

So my question is: how do you decide on the free fraction, which most of us think is the part that should go into the IQ equation to come up with those high IQS?

DR. MAYERS: You are right. To get an IQ that high you have to have a very sensitive virus and a very high drug level.

If we could have slide number 38, first--"Resistance" slide.

[Slide.]

Just to show how we got to serum shift--because it is 99.9 percent bound, but we did do it three different ways. And, basically, if you

add 50 percent serum--both we and pharmacy at Upjohn added 50 percent serum into the cultures, and saw a fourfold shift. We also did an equilibrium dialysis between human serum and 10 percent fetal calf and saw a three to fourfold shift.

So we think it really is about a 3.75-fold is going to be the adjustment for that.

And go back one slide.

[Slide.]

This just shows how we calculated the IQs. And basically we took the $C_{min}$ value. And since all the assays were done with VIRCO, we took the fold wild-type. So this is actually a calculation that could be done in a clinic, in which you would basically take--it's the $C_{min}$ over the IC50 for the wild-type virus, which was about 0.58, times the protein binding factor, which is 3.75 times the fold change.

And, as you can see, to get up above 200 you have to have a very sensitive virus, and a very high drug level.

DR. HAUBRICH: Just to clarify--those fold shifts, were those in the VIRCO assay that was used in the clinical samples here? Or an in-house

different assay?

DR. MAYERS: We did not do any of the samples by in-house. They were all done by VIRCO. And as I showed this morning, we did 100 additional isolates with ViroLogic, and confirmed that they basically give the same regression--obviously variability would be different. But the regression is essentially a one-to-one regression.

And the cut points that we got with VIRCO were identical to the cut points that with ViroLogic for fold change. So we think that they are fairly interchangeable for this drug.

Rich, I would like to identify one potential reason for the outcome. You asked why the HIV-negatives had much higher rash rate potentially than HIV-positives. And there is one

difference that's significant, is the HIV-negative patients have uninduced livers. And so when they get this drug at 500/200, they get significantly higher drug exposures for the first three to four days of drug than the HIV-positive patients, who've all been exposed to protease inhibitors for a long period of time, have fully induced livers. And so there's a much smoother transition onto drug in treatment-experienced patients than there was in the healthy volunteers, where they got three to four times as high levels in the first three to five days.

DR. ENGLUND: Thank you.

Dr. Grant?

DR. GRANT: Yes, I'm still concerned about biases that could have allowed the comparator arm to have poorer virologic responses. And one of them, I understand that it was possible for people to elect to continue their failing regimen and be on the study in the comparator arm on the same PI that they were on initially.

And I wanted to know what proportion of

the RESIST studies had individuals who chose to continue a failing regimen, and whether a sensitivity analysis was done to correct for that bias.

DR. McCALLISTER: Because of the nature of the trial, we had to allow patients to either continue the PI they were on at baseline, or to change it.

When we looked at new versus ongoing comparator PI--I can bring up that slide--

[Slide.]

--if you look across the top you see the total n. You can see the patients who took a new PI versus an ongoing PI here.

In the case of tipranavir, everybody received tipranavir, but if the comparator PI they had indicated was new, they've split out here.

In the case of comparator arm, if the comparator PI they indicated was new, it's also split out here.

"New" doesn't necessarily mean that they were naive to it. It could have been recycled.

"New" simply means it isn't the drug they were taking at baseline.

So these are the actual percentages of patients who took these drugs. And then we have the treatment response of those who were taking those drugs was, as you would expect--can I bring up that slide, please?

[Slide.]

Treatment response of patients who were entirely naive to the pre-selected comparator in the lopinavir stratum, when they pre-indicated that they would prefer to take lopinavir, they had a 53.8 percent treatment response in the tipranavir arm, and a 50 percent treatment response in the comparator arm.

Saquinavir, which has a larger n than indinavir--33 percent and 23 percent--amprenavir, 45 percent and 25 percent.

So when they were entirely naive to the drug that they were taking, you can see the response was similar between the tipranavir and comparator arms for lopinavir, but superior for the

others.

DR. GRANT: Did the FDA do a sensitivity analysis on efficacy, taking into account that?

DR. BHORE: Yes, the numbers we saw--this is exactly--to quote from the protocol--violations data set. The patients who had no new or recycled antiretroviral in the background, or they were continuing their failing regimen--at least the background, in the case of tipranavir, was 96; and in the case of the comparator arm, it was 99, they were continuing their regimen.

But since this was the efficacy was evaluated based on superiority, if we still take into account these patients, then they're essentially comparing tipranavir to a virtual placebo. And so that would show efficacy.

But in our per-protocol analysis that we showed you in one of our slides, we excluded these patients from that analysis, where we said there were treatment regimen violations of about 25 percent-plus in both arms, and we excluded those patients.

So we showed that the treatment effect was positive.

DR. GRANT: Okay. Thank you. I had a

resistance question, as well.

I believe the manufacturer regards L90M to be a key resistance mutation for tipranavir. Could they review the data that L90M affects susceptibility or virologic responses?

DR. MAYERS: Slide 14.

[Slide.]

I get asked this question a lot.

[Laughter.]

So, basically, L90M was included in our key mutations. And it was because when we saw, in the original larger samples, in which they did the panel--the highly resistant viruses--we saw that many of the viruses that decrease susceptibility to tipranavir had an L90M combined with either an 82T or an 84V in those isolates. And so it appeared to be associated with decreased susceptibility--in the small number of isolates we had at that time.

We also noted that when you combined L90M

with those other mutations in our Phase II program, it was associated with decreased virologic responses. And so we kept it in because it was predictive.

And, as you saw, when you use the four mutations in a score, it does score out tipranavir effectively.

On the other hand, when we did the tipranavir score, and we pulled all of the 99 positions individually, L90M is clearly not in the picture. It's not selected in vitro. It's not selected in clinical isolates. So there's actually no--it's neutral as far as selection goes.

It's not associated with phenotype, and it's not associated with viral load responses. And so individually, it has no impact on response.

And the best answer I can give you is: the L90M, when you combine it with an 82 or an 84, it's very hard to get those two mutations into a virus, and it becomes a marker of a very highly mutated virus from a very heavily pre-treated patient to get 82 and 90, or 84 and 90. And so it works

because it's associated with a number of other mutations that do produce resistance.

And so it works when you use it in a score of four, but it falls out when you a multivariate regression and look at all the positions individually. It's probably an association.

DR. GRANT: Mm-hmm. Yet, I mean, there probably are other markers that you could use in addition to L90M. Just because the combined score showed an association between 3 and 4--presumably that means that information about L90M adds some predictive value. But this other data suggests that there's nothing special about L90M. It really is a marker of other mutations.

And I think it would confusing to continue to call this a key tipranavir resistance mutation.

DR. MAYERS: Well, it's a key mutation for protease resistance because, as we've shown, when you have four of them, you essentially have broad protease I can show the slide, if you want. But, basically--if we could have slide--I think it's number 4.

[Slide.]

This shows those four mutations across the whole Phase II, Phase III trial program. And what

you can see is that as you go from zero to three of them, you see a ramping. And it isn't until you get to all four that you see tipranavir resistance.

But for all the other protease inhibitors, when you have more than even one of them you start to see high levels of resistance across the whole panel. So that basically, for whatever reason, they work reasonably well for a doc who needs just something that they can keep in mind.

The 21 mutations at 16 sites we think will be good for resistance reports. And so for the companies that do diagnostics, we're offering it. And we're proposing to actually go forward and do a weighted score, because the 30, 48 and 88 and 50 all actually subtract out of the score if you want to weight them.

But that gets really very complicated for the doc out in the community. I think it's useful for diagnostic companies.

We're trying to find something that was reasonably simple for someone out in the field to use that would accurately predict responses.

DR. ENGLUND: So, we have one more question, really, and then we're going to have to--one more speaker, and that was Ms. Dee.

MS. DEE: Thank you. This is a safety question, again.

I'm just not feeling comfortable, from a community perspective, with the answer that I got about the liver toxicity before. And it's not that this--in my opinion--this drug might not have a place in our arsenal. I think it does.

But I'm feeling like we need to know the hepatic risk as accurately as we can.

And in our FDA materials it says that "At the time of the data submission a substantial number of subjects have not resolved their LFT elevations, and therefore no conclusions can be made about the acute clinical impact of these laboratory abnormalities."

So I just would like to know how many

people are we talking about, and how they're doing now?

DR. McCALLISTER: I think to answer that I'd like Dr. Corsico. And then perhaps for the clinical context you're seeking, Dr. Sulkowski after that.

MS. DEE: Great. Thanks.

DR. CORSICO: The data set that we presented actually extended that cut through September 30th, which is why our data set actually had more pieces. Now, the FDA has made it clear that they were able to do their analyses based on what was submitted through the June 11th submission.

That additional data set allowed us to look to see what we were seeing in terms of clinical outcomes with respect to elevated liver function tests. And in the core presentation, we did show that the majority of patients who developed a Grade 3 or 4 elevation in their LFTs actually continued therapy. There were four of those patients who actually had what was called a

"serious adverse event with an hepatic term." They continued their therapy despite that, and those terms that were reported in the context of that serious adverse event were increased ALTs and an increased bilirubin.

For the patients that discontinued--which was only a quarter of those with the Grade 3/4 elevations, there were five clinical events. Those patients had a case of toxic hepatitis; a case that was reported as "liver failure" which, upon further scrutiny, actually really appeared to be more hepatitis, because the patient was actually re-challenged, developed the same increase in their ALT, became jaundiced and stopped the medication, but completely recovered.

Only one of those patients of those that developed clinical outcomes in the discontinued group actually had a fatal outcome, and that was that co-infected patient with hepatitis B, who had a CD4 count of below 50 starting treatment and then at the time of death.

But I think you raise an important

question. I think we need to put it in clinical perspective, because this is really a risk-benefit issue. And I would appreciate it if we could have Dr. Sulkowski just comment on that, since he is actively treating these patients.

DR. SULKOWSKI: Good afternoon. I'm Mark Sulkowski from Johns Hopkins in Baltimore, and my role there is to provide medical care to persons co-infected with hepatitis C or hepatitis B and HIV. So I run a co-infection clinic at Johns Hopkins.

And, clearly, this issue of liver toxicity comes up in every antiretroviral decision that clinicians make. These decisions may be complex in the setting of a hepatitis C co-infected patient.

I think the important context to keep in mind is that even among hepatitis B and C-infected patients in east Baltimore--and across the world--the leading cause of death remains HIV. Although liver disease is increasingly something we pay attention to, HIV is still driving morbidity and mortality.

So I think both the FDA and the sponsor have done a nice job in giving us a detailed analysis of the potential hepatic risk of this

particular agent--both looking at risk factors--hepatitis C, elevated ALT and CD4--and then also planning additional studies.

But, clearly, as this drug is used in practice, we'll take into account both the HIV disease parameters--CD4, HIV viral load, resistance pattern; take into account their liver disease status--and then, along with the patient, make a decision regarding the risk-benefit assessment. So it will be used individually.

I think the thing that we can do today is provide enough information to clinicians regarding which patients are at increased risk.

DR. ENGLUND: Okay. Thank you.

I know there's more questions, but we're going to have to move on.

The FDA has one more comment--I think Andrea--Dr. James--has a comment. And after that, there's a comment requested by the company.

DR. JAMES: I just needed to make a correction on one of my slides. And I think Anuja's pulling it up so that we can see it.

While she's doing that, I can start described it. It's actually Slide 17 in your packet.

[Slide.]

That's the old slide.

[Pause.]

That was the slide. I'll just verbally tell you what the correction should be. And if we ever get it up, you'll see it. It's Slide 17.

And essentially there was a percentage sign placed there, but the decimal points were not moved. And so it should read: instead "0.5%," "5%;" instead of "2%," "20%."

But the message: "5%" and "20%," versus "0.5%" and "2%"--on Slide 17. But the message is the same: that the n is too small to draw any conclusions from the baseline Grade 1--from subjects who had baseline ALT/AST values over Grade 1.

DR. ENGLUND: Dr. McCallister had another comment.

DR. McCALLISTER: Thank you.

Just before the break we were talking about trough concentrations. And we did delve into our data base at lunchtime, and we were able to determine that we had undetectable trough concentrations in between 2 and 4 percent of patients in the comparator arm at Week 4--out of

all the patients participating in the comparator arm.

And, again, we did verify that they were truly taking their drugs by confirming that they had at least a detectable level, before they would be allowed to participate in the rollover study.

Thanks.

DR. ENGLUND: Thank you.

At this time I'd like to have Dr. Birnkrant issue us our first question, which will give us, as a Committee, time to ask more questions, in fact, about safety and efficacy. So, we still have time for questions, but we need to be

moving on.

DR. BIRNKRANT: Okay. Thank you.

So the first question out of the seven that are presented to you asks for a discussion of risk-benefit. And then we will ask you to vote on the question: whether or not tipranavir boosted with ritonavir has been shown to be safe and effective.

So, as you deliberate, we would like you to take into account some of the bullet points that are in the second part of the question, that is: the inclusion criteria of the trials; the drug interactions; the resistance information and the safety considerations.

So what we're looking for is a risk-benefit discussion prior to your vote.

Thank you.

DR. ENGLUND: And I would like to specify at this time that non-voters not only can discuss, we hope they will discuss. They cannot vote, but they can discuss.

And I would like to start out with

question one by trying to limit some questions first to safety. And then we're going to go on to some of the other issues.

We can go on forever. We don't want to go on forever. But I think, to address the first bullet point, I'd like to discuss--do we want to show Slide 17 first?

We'll show Slide 17 first from Dr. James--the correct Slide 17, pointing out the "5%" and "20%" from Slide 17 of the FDA portion, so everyone can have that.

Okay.

And now we're going to start out the discussion with safety--and I'd like to take some time with safety--and then we're going to move into efficacy for a discussion of Question No. 1.

Dr. Haubrich?

DR. HAUBRICH: Well, I think that the evaluation of safety has to be in the context of the need and the efficacy.

And in my opinion, the biggest need in the clinic today for antiretroviral patients--treatment

of antiretroviral for patients--is for those who have drug resistance.

We've heard data of the increasing rates of treatment-experienced patients and increasing rates of drug resistance. And so I think this is the group of people that we clearly need to have new drugs for.

So the risk-benefit ratio for a drug that treats resistant patients is different than the risk-benefit ratio for treating patients that are naive.

We now have clearly effective, tolerable, safe medications--soon to be one pill, once a day--for naive patients. So the bar would be much higher for that. However, for the category of patients that are being discussed here, clearly the bar is very different.

And I think--in my opinion--the risk that we would tolerate for a treatment for those patients is much higher.

And so I think in the context of the toxicity, I think we're willing to tolerate more

toxicity and complexity in this group of patients, because we do need therapies. And although there are lots of promising drugs on the horizon, when I go to the clinic Monday morning, those drugs aren't going to be available.

DR. ENGLUND: Dr. Fish?

DR. FISH: I would agree with Dr. Haubrich. And I think Dr. Sulkowski said it very well: that it is the HIV that is the driver here in terms of serious morbidity and mortality.

The safety concerns are legitimate, but we have gotten used to having to manage these difficult kinds of not only drug interaction issues, but safety issues. And from what we're seeing here, it seems like most of these things are reversible. Some of them actually improve on therapy. So while the ALT abnormalities are serious, the lipid abnormalities are serious, they are manageable. And I think these are the kinds of complications in this highly treatment-experienced patient population that has become the reality of HIV care in 2005.

DR. ENGLUND: Dr. Rodriguez-Torres.

DR. RODRIGUEZ-TORRES: Well, I am the one that receives the patients when they are jaundiced,

and they have the liver enzymes high. I don't treat them primarily. So I see the complications.

I understand perfectly, and you are perfectly right. There is a need for treatment for patients that have resistance.

If that is a big concern, something that I have asked the FDA people during the lunch period: why you are not considering these to be approved with T-20? That certainly has the best efficacy numbers in all the various examined.

If it is not approved to be used with T-20, at least that has to be very strongly recommended during treatment, because certainly it looks like it was superior.

My concern is with hepatotoxicity. And there's many things here that worry me.

First of all, the prevalence of hepatitis C and B co-infection is much higher that were found in these studies. The prevalence can be as high as

60 percent, especially in minorities; especially in our Baltimore patients, and our San Juan patients. And ALT only is not going to help us discriminate between them, in terms of the severity of the liver disease. We need to do more biopsies, and be much more cautious.

I'm a little bit concerned about scarce information about ALT in patients that have adverse events secondary to ALT elevation, if they also had lipid abnormalities. In this drug it seems that may be an important aggravating factor, with fatty deposition and steatohepatitis.

I'm concerned about so many drug interactions. I don't know how the treaters--the common garden treaters, not the experts that we have here--are going to sort out all these complicated interactions and decide when to decrease doses and when to increase doses.

And certainly, I'm concerned about two areas that we have touched in other parts. They described that they have done studies with methadone drug interactions. If they are not

available pending FDA approval, for consideration of approval--methadone apparently will have to be increased with use of these drugs. And the problem that I see there is that many patients are being treated with methadone, it's another doctor. It's not the HIV treater. How we can manage that?

The other thing that worried me was in women that are on pills and oral contraceptives, they will need to have another barrier, because the levels are going to be affected by the drug. How are we going to deal with that? Because that is another safety issue.

So these are my concerns.

I understand the need, but we need to assess these other problems and at least put together some clear, logical and easy-to-follow--or more easy-to-follow--some kind of paradigm the treaters--the primary treaters--can follow with this drug.

DR. ENGLUND: Dr. Sherman?

DR. SHERMAN: So--I appreciate everything Dr. Rodriguez said, and I guess we think about this

sort of like the parable about the blind men and the elephant.

From the view of the hepatologist, patients with liver disease--end-stage liver disease--are the problem. And in my institution, and among those where I talk to many colleagues who deal with patients with HIV-infected patients, we see lots of patients coming in and dying of end-stage liver disease, with undetectable HIV viral loads.

And clearly recognize that multi-resistant disease is a problem, but it may--as I'll mention in a second--even be a bigger problem as we get into the issue of end-stage liver disease.

So I wrote down a series of points here. I just wanted to run through them.

First: this study has short-term HIV endpoints. We really haven't heard anything about longer-term endpoints. We haven't heard about--at least anything that's convincing--in terms of prevention of opportunistic infections. And certainly, as with many drugs, we haven't heard in

short term studies about long-term survival.

I'm concerned that there's been a failure to address some of the issues that were associated early on with what appeared to be a hepatic signal, even in the controls, the Phase I studies that a high proportion had abnormal liver enzymes. And yet, as planning went forward, it didn't sound like there was enough concern to think about getting liver biopsies to better define sub-populations: those with underlying liver disease, versus those that don't have underlying liver disease. And that certainly decreases my enthusiasm for moving forward as a rapid approval for this agent.

There's the fact that short-term use will not occur. Everyone in this room knows that once these drugs are started, and if they have an effect in a subset of patients, they'll have an effect. At this time they are the last drug, and they're going to be used--this is going to be used for an extended period of time in patients.

And, frankly--and we've had this discussion in this committee before related to

other drugs--the concerns about short-term flares are not the issue with liver disease. The concern is the patient that cruises along at ALTs of two and three and four times normal for years on end. And those are the ones that have more progressive fibrosis, more rapid liver disease.

Just with hepatitis C alone--Dr. Sulkowski recently presented data that showed a much more rapid rate of progression in co-infected patients than in those in singly-infected patients, and recommended more frequent liver biopsies in the HCV mono-infected patients.

I didn't hear any clear plans for future histology-driven analyses.

I think, in the community, there's a very poor understanding of liver injury. And so echoing what DR. Rodriguez said about the people in this room versus those who are out in the real world, there is very poor monitoring of liver disease abnormalities. And this concept that you have to wait to symptomatic is actually one of the biggest issues hepatologists face. Because when you have

symptoms from end-stage liver disease, the game's over. So the time to be worrying about this is well, well before that point.

And the game is over even more, because we are beginning to transplant successfully patients with HIV, but the ones that are not being transplanted now are those with multi-drug resistance who run a risk of breakthrough. So these are the very patients that are going to--at this time at least, based on where we're at with that emerging filed--be the ones that are least likely to be transplanted.

Drug-drug interactions are significant. That's been mentioned here already. And the drug-drug interactions that may lead to increased liver toxicity, again, have not been very well characterized, at least up to this point.

So I think that from the point of view of hepataology--of liver disease--there are still many questions remaining.

DR. ENGLUND: Ms. Dee?

MS. DEE: Thanks.

You know, I think that we do have to look at this, you know, as a risk-benefit sort of "Well, what patients need this? Does this drug

have a place in our arsenal? And what place is that?"

And I think that it does, but I think that given what we've already heard, and given what we've seen, that it may be a limited place--which is addressed in the first bullet about the limited inclusion criteria. So I think obviously we're talking about heavily pre-treated patients. Because I'm not sure that it's been proven that it worked any better in anybody else.

And the drug interactions--you know, I'm reminded, the last time I was a guest on this Committee was indinavir. And they had the ritonavir hearings the next day. And I think the agency--well, the thing was that Abbott was supposed to do educational materials for physicians so that you could try to keep all this straight in your mind when you were prescribing this. And I think that not only do we need to have more tests

on this, but there needs to be education for physicians and patients about what drugs can be taken with this, and what drugs can't; I mean, some easy little pocket card. I don't know, I guess it might have to be long.

I also think that the label should indicate that resistance testing should be done, and that this drug should be indicated for people with certain mutations and not others. And, again--I mean, I don't want to harp on the safety considerations, but you know, I think that if people know ahead of time, then you can't be blamed for not letting them know that something is an issue. And I think that further liver studies are extremely important.

And I'd like to know, I think--it's a question in my mind why I never heard about this rash before, in all the times that I've seen data on this drug.

DR. ENGLUND: Dr. Munk.

DR. MUNK: Yes, I'd like to echo some of the comments about risk-benefit, and how that is

going to be a somewhat different calculation and equation for a drug that's designed for a heavily treatment-experienced population.

But I'm really concerned, after looking at all the data, at the fact that although I think we can characterize the patient population, we may be in trouble trying to characterize the prescribing population.

This is not a drug that can just be turned loose on the prescribing market without an awful lot of information. And, personally, I'm skeptical about the value of the package insert contents. And I'm not really sure how to do this.

I mean, the primary investigators at the various sites presumably know how to monitor for liver enzymes and so on, and presumably know how to treat them. But if tipranavir gets general approval, or accelerated approval, I wonder what's going to happen out there. I think we're still lacking some important data on interactions.

I was concerned that ibuprofen showed up as a drug that was predictable to have an

interaction--and yet there's no study planned on that. And in my mind, if I don't have information that says there's a potentially important interaction here, I'm going to say, "Okay. It's benign." And ibuprofen is certainly something that an awful lot of people might be taking for a variety of reasons.

So, it's a difficult one for me because for the salvage population I wouldn't want to see them denied access to this agent. But I'm just really concerned about whether it's ready for prime time.

DR. ENGLUND: Dr. Wood?

DR. WOOD: I think one of the concerns that we all have in terms of assessing the risk-benefit is that individuals who are heavily treatment-experienced and in need of salvage therapy also tend to be the population of individuals who have baseline elevations in their liver function studies.

What I think is going to be a difficult decision point, given the described hepatotoxicity

is the decision that clinicians are going to face when they do have people who are at the end of the line, without treatment options, who have above Grade 1 elevations in their transaminases.

I don't know what we recommend, because I think there's very, very little data that we can conclude, in terms of the safety in this population. But it's the very population that we're at the end of the line, and they really need drugs--and so do you bit the bullet?

I clearly would urge the pharmaceutical sponsor--since we know that there is this persistent elevation in liver function studies--to generate data that lets us know the magnitude of the elevation over time.

I think we all have different levels of comfort in terms of what we will tolerate as clinicians in terms of a persistent transaminitis. People don't bother--not quite as uncomfortable with persistent Grade 2 elevations. But when you're talking about Grade 3 and Grade 4, that are going to be sustained over months and potentially

even years, with people with ASTs and ALTs in the 400, 500, 600 range, that clearly has, I think, different implications for long-term toxicity.

I'd also be interested--we didn't discuss this earlier--as to whether or not there was any evidence of changes in other parameters of liver function, in terms of coagulation studies in the individuals with prolonged tipranavir exposure.

DR. ENGLUND: Is that a question to the company?

DR. WOOD: Yes--if they can answer it?

DR. McCALLISTER: The answer is no. Patients have AST or ALT elevations. There are only a couple of total bilirubin elevations that were described. And coags were not elevated.

DR. ENGLUND: Thank you.

Dr. DeGruttola.

DR. DeGRUTTOLA: Yes--just reiterating what others have commented on: there does appear to be a patient population that would have a favorable risk-benefit profile for this drug. And the issue, obviously, is how well that group can be

identified.

The benefit that's been demonstrated, of course, is the short-term. And longer-term information will be crucial for getting a clearer sense of who will benefit.

But some other issues, I think, have to do with how well we can predict who will develop the liver or other toxicities, and also how well we can predict who will derive the virological benefit.

There have been analyses that have demonstrated that there are important predictors of some of the liver toxicities. And I think what would be useful is putting those analyses together and getting a sense of how well do you actually predict; how well can you classify patients according to their future risk. The regression analyses themselves don't provide that answer regarding prediction, although it could be investigated.

The other issue has to do with identifying the patients who would be most likely to benefit virologically. Obviously, those are patients who

have some degree of multi-drug resistance, but not very high level resistance to proteases. And Dr. Mayers made a crucial distinction when he talked about the difference between mutations that may have a direct causal impact on efficacy--such as, for example, the 82 or the 84--and other mutations that may be important just by association because they're associated with having mutations that do have that causal effect, even though they themselves don't.

As long as the mix of mutations across patients in the population doesn't change over time, it may not be so crucial to make that distinction and recommendations. However that mix could change. It could be that with different mixes of mutations, it wouldn't be the 90 that would be the most highly associated, but some other mutation that's most highly associated with the others that are bad.

So I think that it is important to understand the causality relationship between these mutations and the amount of resistance. And I also

think that it's useful both to do as many exploratory analyses as possible--of the type that have been done, but others as well--to try and determine what is the best classification of patients that will best predict their ability to respond favorably to tipranavir, and to need tipranavir in order to get a good response.

I think that the analyses that have been done are very useful, and helpful to the Committee in terms of doing the ultimate recommendation. But I think continuing to do analyses that will look specifically at the question of classification: can we classify patients according to how well--what the probability is of the individual patient responding well; not simply that the mean for that group of patients shows a good drop, but that we can classify patients according to their ability to respond well.

Because ultimately, the ability to identify this group with the most favorable risk-benefit ratio will depend on that ability to classify accurately.

DR. ENGLUND: Thank you. I think Victor's done a good job of bridging us over into the efficacy--which, of course, it's totally impossible

to discuss safety and efficacy totally separately.

But before we take a vote on the first section, I would like you to note that if te vote is "yes" we get to discuss a little bit more.

But in terms of the efficacy, I would just like to point out that as a treater, and with a person from my point of view, I'm very anxious to get drugs that I feel are reasonably safe--if I can have a patient profile that distinguishes which patients are likely to benefit.

And in my setting I feel that I can follow my patients. In my clinic I can follow them closely.

Perhaps we need guidelines--and certainly there are guidelines that these kind of patients should be treated by experienced clinicians. This is kind of something that's difficult to enforce. But in this day and age, with HIV physician accreditation, and with kind of the formation of

big-center clinics, this is the kind of thing that would be nice to implement.

So I'd like to ask if there's any question specifically related--or not specifically, but a few more comments or questions related to efficacy?

Dr. Morse?

DR. MORSE: I have a totally biased comment, since one of our major endeavors is to try to set up a national registry for addressing these types of issues.

But one of the concerns that I have is that the drug interaction questions that I think contribute directly to the safety question are helpful in certain settings. But in many cases, the types of patients that we're talking about today are on eight, 12, 15 drugs at the same time. And a large percentage have co-infection.

So while I think pointing out what needs to be done further is very important, the practicality of identifying who is most likely to be safe--which is what Victor was saying--but then once we get beyond that, I think everybody here

feels relatively uncomfortable about how those other patients that get more complex very quickly will be managed. And maybe that might be viewed as one of the follow-up studies, which would be some type of an approach to not necessarily enroll into a study, but have some type of formalized follow-up so that the concerns about long-term use and toxicity can be followed.

I mean, I think that's probably as important as any one specific drug interaction study.

DR. ENGLUND: Dr. Grant?

DR. GRANT: I agree with others that I think that we've seen data that establish a subgroup that is predicted to have a favorable risk-benefit with tipranavir treatment.

But I'd like to hear more about the study that was offered to those with multiple--that is more than two--primary or key PI mutations. I think it's 1182.51.

Because the patients in the RESIST studies really are not the deepest, salvage kinds of

scenarios that there are out there; they're, in fact, patients who have moderate PI resistance. And I do not believe we saw any efficacy data from the .51 study, which would have represented patients who had two or more PI resistance mutations.

DR. ENGLUND: Dr. Birnkrant, is that allowed?

DR. BIRNKRANT: For clarification.

DR. GRANT: I think it is relevant, though. Because the proposed language for the indication is that this is appropriate for salvage settings. And yet the people with the highest level resistance were excluded from the trials that are being presented.

DR. MAYERS: This is Doug Mayers.

I'd like to have Slide 32 from the "Resistance" set.

[Slide.]

And basically, as you know, after two weeks we added tipranavir to the other PIs and got a 1-log response, which then began to fall off in

the majority of these patients; only about 12 percent of them received T-20 in this cohort. So when you get down to it, basically all of the effect we saw in this study was tipranavir in all the arms.

It's very hard to get conclusive efficacy conclusions, because after the four-week time point, since this was a PK and safety study, the docs and patients were allowed to switch. And so the arm people were in changed sometimes three times out to six months as to what they were combining with the tipranavir.

So what I can tell you is that tipranavir gave a log of activity. There was a small percentage--maybe 10, 15 percent of patients--who got a durable, sustained drop. But after four weeks you start to see a loss of virologic activity, basically because they had tipranavir, and most of these patients had less than one active background drug to support it.

I mean, that's the fundamental problem you get into in this deep salvage group of patients.

It's not that tipranavir isn't active. It's an active drug. But it needs one or two additional active drugs to partner with.

And the one that we've seen good anecdotal response with has been the T-20-naive patient who gets tipranavir in this setting, and does go undetectable.

DR. ENGLUND: Thank you.

Dr. Gerber?

DR. GERBER: Yes, just briefly.

As I'm listening to everybody, I think the biggest problem here is that what we don't have is hard data showing that there's improved survival, or a decrease in opportunistic infections associated with the therapy. I know it's a short-term therapy, but I think nobody would deny that this drug should be on the market--if there was survival data, or there was actually an improvement in the opportunistic infections.

So that's what we're struggling with. It's a drug that has some toxicity, and clearly virological efficacy, but somehow--maybe we haven't

followed these people long enough.

So that's what I'm struggling with. I'm listening to everybody, and I agree that we do need a drug for the multi-drug resistant patient. I mean, those are the ones I see in the clinic. But I certainly would be a little bit more cheerful about this drug if we had some hard data that, in the long term, I'm making a difference.

DR. ENGLUND: Thank you.

Dr. Birnkrant, have we had some discussion so that we could put the first part of votes? So we could potentially discuss the second part?

DR. BIRNKRANT: That would be fine.

DR. ENGLUND: At this point I'd like to go around the table. I think actually we're going to--you're going to have to help remind me who can vote. But I think I have this written down here.

And we're going to go around the table, and I would just like you to address the first question, which is: do the data demonstrate that tipranavir-ritonavir combination is safe and effective for multi-drug resistant HIV-1-infected

population? And if no, what additional data are needed?

If yes, I think we could move that to a separate discussion. And we'd like to do this relatively quickly.

So we'll start with Dr. Wood.

DR. WOOD: I will say yes, with conditional specifications.

DR. DeGRUTTOLA: I would say yes--also with conditional specifications.

DR. ENGLUND: Dr. Rodriguez-Torres?

DR. RODRIGUEZ-TORRES: No.

DR. ENGLUND: And what additional data would you like? You've said some before, but--

DR. RODRIGUEZ-TORRES: All the drug interaction studies that we have mentioned; evidence of histology in patients--follow-up with histology; and better definition of the ALT elevation and the outcome, in terms of liver disease.

DR. ENGLUND: Dr. Munk?

DR. MUNK: Yes, with concerns.

DR. ENGLUND: Dr. Sherman?

DR. SHERMAN: No, as a rapid approval at this time--pending longer-term data with clinical

outcomes and with better characterization of liver disease.

DR. ENGLUND: Dr. Gerber?

DR. GERBER: Yes, with concerns, as well.

DR. ENGLUND: Dr. Washburn?

DR. WASHBURN: No, with a need for long-term efficacy follow-up.

DR. ENGLUND: Dr. Grant.

DR. GRANT: Yes, with concerns.

DR. ENGLUND: Dr. Miller?

DR. MILLER: Yes, with the concerns.

DR. ENGLUND: Dr. Maldarelli?

DR. MALDARELLI: Yes, with reservations.

DR. ENGLUND: Dr. Morse.

DR. MORSE: Yes, with the concerns I mentioned.

DR. ENGLUND: And Dr. Capparelli.

DR. CAPPARELLI: Yes, with concerns.

DR. ENGLUND: Dr. Hall.

DR. HALL: Yes, with concerns.

DR. ENGLUND: And I'm allowed to vote.

Yes, with concerns--and probably the same concerns we all are talking.

That is 11 voting yes, so the yeses carry this in terms of--three nos, 11 yeses.

For those who said "yes," there was a high concordance rate of additional concerns, and severe concerns. And I think now it would be very good it we could start perhaps at the other end of the table--with Dr. Hall--and if you could please help us with what are your highest degree of concerns. And what would you recommend?

The question specified on the FDA proposal says: "Address the appropriate population, based on the other problems." But the other issues are perhaps what you would like to address, including limited inclusion criteria--which as been discussed; interactions of drugs; resistance and/or safety.

Dr. Hall?

DR. HALL: Well, I think the concerns are

the ones that everybody's mentioned: simply the long-term outcomes and how, in practice, things will be managed on a daily basis.

I don't think that there's a lot more to say about that. I think it's been covered pretty well.

DR. ENGLUND: Dr. Capparelli?

DR. CAPPARELLI: I would just concur, and especially with the focus on the expansion of use with other drugs; you know, the limited scope of the criteria for this particular study.

I noted, in particular, that if you looked at the common combinations there weren't--you know, it was everybody was on tenofovir, no one was on NNRTIs--or there were very few, if at all; and very few on thymidine-containing regimens--at least in terms of the common.

So even within the background therapy there are issues that would be of interest, and that may relate to safety issues as well as efficacy issues.

DR. ENGLUND: Dr. Morse?

DR. MORSE: I think my main concern in discussing a patient what the benefit of this drug would be is that I could feel confident saying it

has some activity, but not that it's been compared against something where you could say the percentage of increased activity is X.

So my concern is that some type of a follow-up study be developed concurrent with these last couple of years; for example, rather than the control PI arm, that arm might have been a control PI that had therapeutic drug monitoring, and dosage adjustment of those PIs.

Or there is certainly an interest on the part of the AIDS clinical trials group to put together, as a number have said, maybe one, two, three or more investigational drugs to figure out the best way that tipranavir can be used.

So I think there are additional follow-up studies.

DR. ENGLUND: Dr. Maldarelli?

DR. MALDARELLI: I think the durability of this agent remains uncertain.

I think it's obvious from the studies that it has efficacy, since new resistance mutations emerge on it. But how long one can derive any virologic benefit from it remains uncertain.

So I think some studies directed toward that would be important.

I think in treat patients, we obviously balance that with toxicities. In fact, I think what we do most is manage toxicities. And learning more about what these are like in the longer term are also quite important.

DR. ENGLUND: Dr. Miller.

DR. MILLER: Yes. I mean, basically I think that's the major issue: sort of the long-term effect of the liver toxicities.

It's really too bad that the 48-week data was not available to be reviewed at this time, because I think that may have clarified some of the longer efficacy questions.

I also think that with regard to the rash--and I know the company--the sponsor--did mention that they had some studies planned, but I

think that's an area that requires clarification as to what kind of clinical management? Do patents have to be taken off, or can they be treated through? And what some of those risks may be, especially in patients with different levels of CD4 cells and all of that.

In terms of how this is going to be used out there, I mean there have been so many discussions about the expertise required to treat HIV, and I don't know if this group--I mean, I think this group can say: yes, treatment of HIV requires a high level of expertise, and encourage that to happen. But, unfortunately, this agency does not regulate how the treatment is actually happening. There's other groups that do that.

So, I think maybe just a recommendation supporting that is something that just doesn't hurt to put in there--not in the label, obviously, but out there.

DR. ENGLUND: Dr. Grant?

DR. GRANT: Yes, I think it should be emphasized that these patients, and this drug

should be restricted to clinicians who have clear expertise in HIV and antiviral management. And this wouldn't just be for this drug, but these patients in general should be handled.

I'm concerned that the evidence is not yet sufficient to clearly identify a favorable risk-benefit in women. And I'm particularly concerned that the rash may indicate a serious serum toxicity, and that this was under studied in the Phase III trials in women--and particularly women on birth control pills.

So I would encourage the manufacturer and the FDA to work on establishing a clear line of evidence establishing positive risk-benefit in women.

DR. ENGLUND: Dr. Washburn.

DR. WASHBURN: I remain unconvinced that the risk-benefit ratio is acceptable, even in the salvage situation, based on a fundamental lack of satisfaction with a short-term, unblinded study.

DR. ENGLUND: Dr. Sherman--short summary.

Yes--well, I guess I'm supposed to skip

you, but--

DR. GERBER: Are you skipping me?

DR. ENGLUND: No, I'm not skipping you. The order's wrong.

Dr. Gerber--sorry.

DR. GERBER: Oh, that's okay. I mean, if you want to skip me, it's fine.

[Laughter.]

DR. ENGLUND: No--you said "yes." I don't want to skip you. I'm sorry.

DR. GERBER: Again, the concern to me is not having a clinical outcome, and this might be something for future clinical trials, where a drug that's going to be proposed for very advanced patients should have, as a primary outcome, some clinical aspect to it, rather than purely virological aspect--especially if the drug has some toxicity

And I'm also concerned about drug-drug interactions--specifically, the lipid changes which are quite significant with this drug. And we really have no idea how to treat it at this point.

So I think it would be important to have drug-drug interaction studies that basically look at the other statins beside the torvastatin, or fibrates, to see if we can use them together with this medication so we can appropriately the lipids that are going to be quite significant problems.

DR. ENGLUND: Dr. Sherman--who voted no.

[Laughter.]

DR. SHERMAN: Do I have to wear that as a crown now?

[Laughter.]

DR. ENGLUND: That means you have to be shorter.

DR. SHERMAN: In terms of the appropriate population, obviously those with resistance patters that are consistent with the inclusion criteria; and in terms of pre-treatment status, preferably those with normal or near-normal liver enzymes--if possible, understanding that that may not be always possible; and if those enzymes are elevated, then a recommendation that those patients be fully evaluated for the amount of underlying, primarily

fibrotic liver disease that they already have, because the risk-benefit equation is likely very different in those that have a Metavir Stage 0, 1, 2 disease, versus those that are pre-cirrhotic and cirrhotic.

DR. ENGLUND: Dr. Munk?

DR. MUNK: I think we need better characterization of the drug-drug interactions; better understanding of the treatment with tipranavir of co-infected, hepatically-impaired population--and women. And we need better characterization of the resistance information so that in that .51 study, where there was about a four-week 1-log improvement in viral load, and then a decay, can we really identify which protease mutations will cause that? Will any other active drug extend the benefit in that situation?

We need to know more about that.

DR. ENGLUND: Dr. Rodriguez-Torres, you've given us some ideas earlier, but--

DR. RODRIGUEZ-TORRES: Yes, I have spoken too much, for the first time.

[Laughter.]

DR. RODRIGUEZ-TORRES: [Laughs.] Nothing else to add. I agree with what Ken said about the