DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE (AVAC) MEETING

Tuesday, May 13, 2003

8:00 a.m.

Holiday Inn Gaithersburg

Two Montgomery Village Avenue

Gaithersburg, Maryland

PARTICIPANTS

Roy M. Gulick, M.D., M.P.H., Chair
Tara P. Turner, Pharm.D., Executive Secretary

MEMBERS
Victor G. DeGruttola, Sc.D.
Janet A. Englund, M.D.
Courtney V. Fletcher, Pharm.D. (Consumer Rep)
Princy N. Kumar, M.D.
Wm. Christopher Mathews, M.D.
Kenneth E. Sherman, M.D., Ph.D.
Lauren V. Wood, M.D.

ACTING INDUSTRY REPRESENTATIVE (Nonvoting)
Eugene Sun, M.D.

CONSULTANT (Nonvoting)
Joel Morganroth, M.D.

CONSULTANTS (Voting)
Douglas G. Fish, M.D.
D. Roger Illingworth, M.D., Ph.D.
Peter R. Kowey, M.D.
Rory P. Remmel, Ph.D.
Thomas R. Tephly, M.D., Ph.D.
Ronald G. Washburn, M.D.

PATIENT REPRESENTATIVE (Voting)
Matthew Sharp

FDA
Debra Birnkrant, M.D.
Mark Goldberger, M.D., M.P.H.
Kendall Marcus, M.D.
Lisa Naeger, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GULICK: Good morning and welcome. I am Trip Gulick from Cornell University. I am pleased to welcome everyone to today's Antiviral Drugs Advisory Committee Meeting.

We will start off by introducing the members of the Committee. We will start with Dr. Sun over in this corner. Please state your name and your affiliation.

Introduction of the Committee

DR. SUN: Eugene Sun, Abbott Laboratories.

DR. MORGANROTH: I am Joel Morganroth, a cardiologist in Philadelphia associated with eResearch Technology and the University of Pennsylvania.

DR. KOWEY: Peter Kowey. I am an electrophysiologist and cardiologist at Thomas Jefferson University and Lankenau Hospital in Philadelphia.

DR. FISH: Douglas Fish, Division of HIV Medicine, Albany Medical College.

DR. WASHBURN: Ron Washburn, infectious-disease doctor from LSU in Shreveport.

DR. ILLINGWORTH: Roger Illingworth, a

lipid specialist from Oregon Health and Science University in Portland, Oregon.

DR. REMMEL: I am Rory Remmel, Department of Medicinal Chemistry, University of Minnesota, specialties in clinical pharmacology and AIDS drugs and drug metabolism.

DR. TEPHLY: Tom Tephly, University of Iowa, Department of Pharmacology.

DR. MATHEWS: Chris Mathews, University of California, San Diego.

DR. FLETCHER: Courtney Fletcher, University of Colorado Health Sciences Center.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

MR. SHARP: I am Matt Sharp. I am a thirteen-year survivor of AIDS.

DR. ENGLUND: Janet Englund, Pediatric Infectious Diseases, University of Washington and Fred Hutchinson Cancer Center.

DR. KUMAR: Princy Kumar, Georgetown University, Washington, D.C.

DR. DeGRUTTOLA: Victor DeGruttola, Harvard School of Public Health.

DR. HAMMERSTROM: Tom Hammerstrom, statistician, FDA.

DR. NAEGER: Lisa Naeger, microbiology reviewer, FDA.

DR. MARCUS: Kendall Marcus, medical reviewer, FDA.

DR. BIRNKRANT: Debbie Birnkrant, Division Director, Division of Antiviral Drug Products, FDA.

DR. GULICK: Thank you. Tara Turner will now read the conflict-of-interest statement.

Conflict of Interest Statement

DR. TURNER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

Dr. Joel Morganroth will be permitted to participate in the committee's discussions. He is excluded from voting.

Dr. Roy Gulick has been granted a waiver

under 18 U.S.C. section 208(b)(3) because his employer receives research funding from two competitors. Each firm provides less than $10,000 a year. And, for serving as a consultant to two competitors. He receives less than $10,000 a year from each firm.

Dr. Courtney Fletcher has been granted waivers under 208(b)(3) and 21 U.S.C. section 355(n)(4) for owning stock in a competitor valued between $25,001 and $50,000.

Dr. Ronald Washburn has been granted waivers under 18 U.S.C. 208(b)(1) and 21 U.S.C. section 355(n)(4) for owning stock in two competitors. The first stock is valued from $25,001 to $50,000 and the second stock is valued from $50,001 to $100,000.

Dr. Peter Kowey has been granted a 208(b)(3) waiver for consulting for two competitors. He receives less than $10,000 a year from one and between $10,001 to $50,000 a year from the other firm.

Dr. Roger Illingworth has been granted a 208(b)(3) waiver for consulting for a competitor for which he receives from $10,001 to $50,000 a year. And, for speaking for a competitor for which

he receives from $10,001 to $50,000 a year.

Dr. Kenneth Sherman has been granted a waiver under 21 U.S.C. section 355(n)(4) for owning stock in a competitor worth between $5,0001 and $25,000.

Dr. Victor DeGruttola has been granted a 21 U.S.C. section 355(n)(4) waiver for owing stock in a competitor valued at less than $5,000.

Dr. Princy Kumar has been granted a 21 U.S.C. 355(n)(4) waiver for owning stock in two competitors. The first stock is worth from $5,001 to $25,000 and the second is worth less than $5,000.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30, of the Parklawn Building. The signed disclosure statements are available for public review at this meeting.

Lastly, we would also like to note for the record that Dr. Eugene Sun is participating in this meeting as the Acting Industry Representative, acting on behalf of regulated industry. Dr. Sun is an employee of Abbott Laboratories.

In the event that the discussions involve

any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. GULICK: Thanks very much.

I am now going to turn to Dr. Catherine McComus from the University of Maryland who is going to tell us about a project that is going on in today's meeting.

DR. McCOMUS: Thank you and good morning. My name is Katherine McComus. I am a faculty member at the University of Maryland. I am here today to ask for your assistance on a study that I am conducting with collaborators at the Food and Drug Administration that examines conflicts of interest and FDA advisory-committee meetings.

This study is being conducted across several centers at the FDA and at multiple

meetings. It is an attempt to gain an idea of what people understand and know about the procedures that the FDA uses to monitor and manage real or potential conflicts of interest of its advisory-committee members.

So I am responsible for all of these grey questionnaires that are on your chairs in the audience and I have also distributed a separate questionnaire to advisory-committee members. I am two short, but I will get you tomorrow.

I would like to ask that you take about fifteen minutes today, if you have an opportunity to complete the questionnaire. There is a box at the registration desk where you can drop it in. If you don't have a chance to complete it today, there is a business reply envelope and you can complete it later and mail it back to me postage-paid. I will also be around today and tomorrow for those of you that are here tomorrow to answer any questions that you may have about the study.

Again, thank you very much for your time. Your responses are very important. They increase the validity and reliability of the results and really will help us to offer recommendations on how we can improve overall satisfaction with the

advisory-committee function.

Thank you.

DR. GULICK: Thanks. I think an informed consent is not required.

DR. MCCOMUS: No, but it has followed institutional review-board procedures.

DR. GULICK: We had one committee member joining late. Dr. Wood, could you just introduce yourself and your affiliation?

DR. WOOD: Good morning. Dr. Lauren Wood, National Cancer Institute.

DR. GULICK: Thanks.

We will turn now to Dr. Birnkrant from the agency for some introductory remarks.

Introductory Remarks

DR. BIRNKRANT: Good morning.

[Slide.]

I would also like to welcome our advisory-committee members, consultants and guests to today's advisory-committee meeting on atazanavir, Bristol-Myers Squibb's once-a-day protease inhibitor for HIV treatment.

At this point, I would like to commend Bristol-Myers Squibb for their drug-development program for atazanavir. They not only conducted

studies in treatment-naive subjects but also in treatment-experienced subjects and used comparators such as nelfinavir, efavirenz and Kaletra, all widely used in potent protease inhibitors to have a better understanding of how this drug fits into the armamentarium of drugs for HIV treatment.

[Slide.]

Prior to beginning my comments on today's topic, I would also like to commend the FDA reviewers for their time and efforts in preparing for this advisory committee. They had to review more than nine clinical studies and more than forty clinical pharmacokinetics biopharmaceutics studies as well as other data in preparation for today's meeting and in order for us to take a regulatory action within a six-month time period.

With regard to the current marketed protease inhibitors, there are six; two formulations of saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and ritonavir-boosted lopinavir. This class of drugs, the protease inhibitors, have class effects that include metabolic dysregulation manifested by lipid elevation, lipodystrophy and cases of diabetes and hyperglycemia.

[Slide.]

How, then, is atazanavir the same and how is it different compared to other protease inhibitors. Well, with regard to class effects, and you will be hearing a lot about this morning, treatment with atazanavir resulted in less of an increase in lipid parameters compared to nelfinavir in Phase II studies.

This favorable finding was confirmed in Phase III clinical trials.l However, cases of lipodystrophy and diabetes were still seen in the atazanavir database.

[Slide.]

How else is atazanavir the same and how is it different compared to other protease inhibitors on the market? The most common adverse event seen in the database was hyperbilirubinemia. This was investigated extensively and found to be associated with UGT 1A1 inhibition which is similar to that seen with indinavir. However, the incidence of hyperbilirubinemia with atazanavir was much greater occurring in more than 75 percent, all grades 1 through 4, and grades 3 through 4 ranged between 20 and 50 percent whereas the incidence with indinavir is about 10 percent.

With regard to cardiac conduction, atazanavir had dose-dependent and concentration-dependent effects on the TR interval that were generally mild and reversible. In addition, there were effects seen on the QT interval and this will be discussed more extensively by the applicant, the agency and our consultant, Dr. Morganroth.

With regard to resistance, atazanavir has a unique resistance profile in naive subjects. Dr. Lisa Naeger will elaborate on this.

[Slide.]

With regard to efficacy, this was an extensive database that was reviewed for today's advisory-committee meeting. The agency reviewed two principal studies, study 034 in naive subjects that contained 48-week data and used efavirenz as a comparator. Study 043, which was conducted in treatment-experience patients and used Kaletra as a comparator, extensive data from Phase II trials 007 and 008 with rollover studies that contained more than 48-week data.

Given that we received for review 48-week data in the naive patient population and more than 48-week data in Phase II trials as well as 24-week data from 043, would we consider taking a

regulatory action on this application. This application will be considered for traditional approval as opposed to accelerated approval because, as you are all familiar with our paradigm with regard to accelerated approval, we generally only review 24-week data and the applicant has exceeded this.

I would also like to comment on Study 045 which was conducted in a different population that is highly treatment experienced. Because this used a different regimen--that is, a ritonavir-boosted regimen--and because only 16-week data were submitted for review, this study will only be considered for a safety review as opposed to efficacy.

So, just to summarize, the agency considered the two principal studies 034 and 043 as well as Phase II clinical trials 007 and 008 plus their rollover studies as we prepared for today's advisory-committee meeting with regard to efficacy. With regard to the safety that we will be presenting, we considered all the clinical trials in the database.

[Slide.]

So what we will be asking the advisory

committee today will be issues related to the safety and efficacy of atazanavir and, as the advisory committee deliberates, we will ask them to consider the adverse-event profile of this drug; namely, the hyperbilirubinemia seen with atazanavir, effects on cardiac conduction and effects on metabolic parameters including lipid effects.

In addition, we will be asking the committee to comment on the results in the clinical trials seen in the various populations studied as well as a resistance assessment.

[Slide.]

Turning to the agenda for today's committee meeting, following my remarks, Dr. Morganroth will be presenting a primer on evaluation of QT intervals. This will be followed by the Bristol-Myers Squibb presentation which will then be followed by clarifying questions. After our break, the FDA will present--Drs. Marcus, Hammerstrom and Dr. Lisa Naeger will give the FDA presentations. This will be followed by questions.

After lunch, there will be an open public hearing at approximately 1 o'clock. I will then give the charge to committee and this will be

followed by questions to the committee.

Thank you very much.

DR. GULICK: Thanks, Dr. Birnkrant.

We will turn now to Dr. Morganroth to give us a primer on the evaluation of the QT interval.

Evaluation of the QT Interval

DR. MORGANROTH: Good morning.

[Slide.]

I am not sure what a primer is but I will be happy to give you a few minutes of some experience and background in the QT interval which is obviously something you have all been aware of as an important issue in the development of noncardiac drugs and particularly relevant to the safety issues.

[Slide.]

The reason that the QT interval was such a hot topic and is of such importance for developing drugs in terms of their safety profile is because of the concern that drugs that prolong the QTc duration on the electrocardiogram increase the risk of an uncommon to rare event known as torsades de pointes, which is a polymorphic ventricular tachyrhythmia that sometimes can be asymptomatic but often can lead to syncope and occasionally be

fatal in a fair number of cases.

Most of the cases in the literature are thought to occur at fairly prolonged durations of the QT interval. The normal is around 440 milliseconds but not all cases are greater than 500 milliseconds as many clinicians might think.

[Slide.]

This is an example of torsades de pointes that the division provided me that really shows the twisting of the pointes. It is obviously a very fast rhythm that would not likely provide sufficient output of blood to keep the brain happy for a while and that would, of course, cause the CNS symptoms to death.

[Slide.]

Prolongation of the QT interval by noncardiac drugs is the commonest cause of drug delays in development, nonapprovals and withdrawal from the market. So I learned in January, when Dr. Temple provided that information--I thought it was something more likely to do with the liver but it turns out that QT is now risen to the top of the list.

Here is a example of the types of drugs that have been withdrawn from the market in the

last several years. You can see they span a great number of therapeutic categories.

[Slide.]

The probably prototypic noncardiac drug that caused everyone to focus in on the QTc interval as am important safety feature was terfenadine, a non-sedating antihistamine, when one looks at the effect, the magnitude of the effect, on the QTc duration at the usual clinical dose, was approximately 6 milliseconds. That was determined solely by the use of digital-manual ECG analysis after the drug was on the market and there were many cases of torsades, prolonged QTs and death reported.

It turns out, however, that this is the average change over the extent of exposure. If one looks at the maximum change at either Tmax or probably around Cmax, it is around 18 milliseconds. These numbers are important because the magnitude of effect is related, one thinks, to the degree of risk and there are now some regulatory suggestions about how much that magnitude imparts to risk in terms of determining a risk/benefit duration.

With metabolic inhibition of the parent compound, terfenadine, and prohibiting it going to

its acid metabolite, there can be as much as a 50 to 100-millisecond effect in such individuals. With only the reduction of minimal symptoms as the benefit and the potential risk of torsades, death, the drug was removed from the market, particularly since the acid-metabolite, fexofenadine, does not bear any of the blockade of the HERG channel or QTc effects.

[Slide.]

There are many drugs in many categories that are known to affect the QTc interval. I have listed them here on the board. They are very widespread. I have only given a few examples of each. The list actually fills a board. There are over 100 drugs that have been reasonably well characterized.

Some of the drugs have been released on the market in the last couple of years that are clearly ones that prolong the QT interval because of risk/benefit relationships being ones that permit such use.

[Slide.]

The primary effect of the drugs that generally affect the QTc interval on the electrocardiogram as demonstrated in that

therapeutic list is by blocking the IKr HERG-related ion channel. This effect is a primary effect. However, a prolongation of the QTc interval doesn't affect cardiac function. The heart operates as a pump perfectly well, causes no symptoms, and, under the presence of some modifier will, in fact, generate torsades.

That modifier can be a Form Fruste HERG mutation, someone with a subclinical primary prolonged QT syndrome and the two together can, of course, tip the person over the hill and produce torsades.

Obviously, if you can also mimic such effects with bradycardia that prolongs that QT or metabolic conditions like hypokalemia, particularly ischemia, atrial fibrillation. Women tend to be more sensitive to QTc drugs. Their slope is larger in terms of the amount of drug and the degree of the QTc prolongation. Obviously, concomitant use of drugs that also prolong the QT in combination is probably an important common cause of this torsades effect in the market.

[Slide.]

Now, the ECG is complicated in terms of the various aspects that you will be dealing with.

The PR interval, which is the AV-nodal conduction, is something that will be discussed today because this drug that is under consideration does affect conduction. It has an effect on calcium ions and, perhaps, a small effect on the sodium ion.

The QT interval which begins at the beginning of the QRS and ends at the end of the T-wave, the so-called QT, is made up of the depolarization and repolarization--JT is the repolarization phase--and, therefore, one might ask why aren't we dealing with JT if we are interested in repolarization as the effect of the potassium channel, principally.

QRS and the QT interval has been the historic measurement technique and is the best we have. No one believes, in fact, that the QT interval that is measured simply on the 12-lead electrocardiogram is a great index of what is going on with the ion channels and the potential cardiac safety risk, and there are many proposals for looking at various forms of areas and parts of the T-wave and the ST T-wave segment.

However, clinically, the QT interval is what is commonly validated because of all the historic drug effects that have been determined by

that simple method. Of course, we have a great deal of regulatory and clinical experience, epidemiologic experience, with that simple measurement. So, until one has more validated information on using what is likely to be a better measure of cardiac repolarization than the QT, we are sort of stuck with that.

But there are lots of different proposals out there as to what could be used but we are really left, as I said, with the QT interval.

[Slide.]

In November of 2002, the FDA and Health Canada printed the new concept paper which is one in a series of three regulatory guidances stemming from 1996 when CPMP, the European FDA equivalent, published its Points to Consider in this field. Health Canada produced its draft guidance in March of 2001. As these guidances have come along, they have become more granular, more recipe-like, in terms of detailing how one wants to determine cardiac safety as measured by the electrocardiogram.

I think that has happened because, despite the 1996 Points to Consider, there has been continued lack of robust definitive understanding

of ECG effects during many development programs.

The guidance document, or the concept paper, in November 2002 is under review in ICH. I have just taken a couple of comments from it that I thought were relevant. First is that there is a great request, if you will, or urgency, to record ECGs digitally, process them digitally and store them digitally, rather than on pieces of paper with all the obvious limitations that paper has compared to electronic data.

The specificity of using a central ECG laboratory, very much like everyone does with blood tests, is obvious because of the great variability of methods of reading and determinations of morphological interest.

Paper ECGs are fine when digital is not possible or practical. These can easily be digitized or digitally dealt with as analysis. It is clear from all the guidance documents that one should be using a manual method of determining the duration of the intervals, PR, QRS, QT, heart rate, on a digitizing board or with electronic digital data on screen with electronic calipers.

The possibility of using automatic computer readings of interval duration which are

widely understood to not be accurate except in perfectly normal electrocardiograms may be fine for safety analysis. They tend to overread and give longer numbers and shorter numbers and so, for screening for safety at the sites during the clinical trials, that is quite appropriate. But for centralized data, I think the manual data is important.

These are principles that, perhaps, you will look at when you determine whether the definitive trial that Bristol-Myers has conducted today--I think is called 076--how well they followed some of these principles.

The guidance document, also, and this is really the biggest change from any of the previous ones, is actually suggesting--probably the word "require" is not out of place--an intense or thorough or definitive Phase I trial to rule out a 5-millisecond effect for all bioactive agents and even for any agent that is on the market that is brought back for a new indication or for a principal change.

The reason for this is because one really needs to determine whether the drug has a QTc liability or not in order to enter that into your

risk/benefit analysis. It is very difficult, because of the large degree of spontaneous variability, to be very definitive about that in studies with small sample sizes that are traditionally done in Phase I or in Phase III with limited ability to get electrocardiograms where, also, particularly in this particular therapeutic group, it is very difficult to have negative controls, placebo controls.

The important design features that have been added to this and one that has been somewhat controversial is the requirement of using assay sensitivity, a positive control, that one of the arms in this definitive trial should be a drug known to produce a 5-millisecond effect on the QTc duration so that, if you think your drug is the same as placebo--that is, having no effect on the QTc, in the same study, one must show that you were able to detect the 5-millisecond effect of a positive control drug.

This, of course, really does produce assay sensitivity and make the data very easy to be definitive, to be certain about the design characteristics.

The final addition, to show you the

concern of the agency about this issue of QTc effects, electrocardiographic effects of new drugs, is that here is an instance where the FDA now wishes to see, particularly for definitive trials, the actual raw data. They want not just the SAS tables with the results, if you will, of the study, but they actually want to have sent in the EKG wave forms, digitally sent in and annotated so one can see where the central laboratory actually measured the Q and the T-wave because the end of the T-wave, as you all know, is not so easy. That is why the manual measurements are required. That, of course, should be in XML.DTD file. That was published in the Federal Register just a few days ago for comment, the final form that they want to see this in.

[Slide.]

This slide is probably the most important one to consider as you review 076 and as you review trials in general to determine whether they are definitive or not because the issue about QTc duration is there is such a high degree of spontaneous variability in QTc durations from almost minute to minute, the average being about 75 milliseconds in an individual over a day, yet if

we are looking for a small signal that might have clinical significance at 5 or 10 milliseconds from a regulatory perspective, how does one overcome these sources of variability?

The first way to do that is to make sure that you have an ECG measurement method that is accurate. You want to get accurate data. Again, that speaks to the manual, digital validated method. The second issue is to make sure you correct for the QT interval. Remember that the QT interval varies with heart rate so, if you start with someone who has a tachycardia and you give them a drug like an antibiotic and you let their fever and their pneumonia get cleared up, and they now have a slower heart rate, they are going to have a longer QT by definition because, as the heart rate slows, the QT increases.

So it is very important to correct the QT to the QTc. One of the biggest issues you need to look at today is what correction formula is the one to use and which is the appropriate one in order to determine whether the QTc as found is correct or not.

The next issue is how many measurements you make. It is absolutely inadequate to do one

EKG at baseline and one EKG on drug which is often typically done. What you need to do, and I believe the frequency has to cover clearly the extent of exposure of the drug and its metabolites, account for diurnal variation. Therefore, you need EKGs very similar to a PK profile, at least 10 to 20 a day in the range at baseline and then, of course, at steady state or at first dose if it is only a single-dose-appropriate study.

The sample size, in order to have enough power to detect 5 milliseconds because of the high variance is usually at least 30 patients per arm. Usually, I would recommend 40 because half the population it would be nice to be women because they do have increased sensitivity and, therefore, you would have 20 women and 20 men to be able to do a gender analysis.

Volunteers are fine. One doesn't have to try to put in heterogenous patients with the disease under study. It is very difficult to do such large studies with the target population. We believe that if you, with a definitive study in volunteers, see no QTc effect, no effect on cardiac repolarization, then the likelihood of seeing it in higher-risk patients such as ones with cardiac

disease should be very remote.

Important in a trial is to look for dose effects. The doses selected for the drug under consideration should be at least two to look at a dose effect. One of the doses should be able to cover the expected or theoretical, I should say, maximum concentration that might occur in the public.

For example, if a person takes an extra pill and happens be on a metabolic inhibitor, or two, for the drug, one needs to be certain that they have evaluated that potential concentration. That usually means that the second dose has to be at least three to five times, as a guideline, the therapeutic dose. If you can get up to 10X, then the potential of this supertherapeutic dose covering any potential exposure is very clear.

Finally, you need control groups. Without a placebo, it is difficult to determine the effects of spontaneous variability. I have already mentioned the importance of the positive control for assay sensitivity.

[Slide.]

The corrected QT interval is an important controversial topic. I will tell you that I think

there is going to be a great deal of resolution about this, or at least a lot more data than we currently have, at the end of this month when the GU and Cardiorenal Advisory Committee have a public meeting to discuss two applications in which all of these correction formulas that are on this slide were actually applied in a positive-controlled, negative-controlled, definitive QT dataset.

The Bazett's correction formula is what is traditionally, in all the EKG machines that everyone uses in healthcare because that is sort of the historic standard, there is no one, I believe, that would argue that this is the correct, or the best, or the preferred, correction factor.

That is important for this committee because I believe that the Bazett's formula data should be looked at with minimal interest. The maximum interest should be on the Fridericia's formula, particularly for drugs that have an impact on the heart rate. Any drug that increases the heart rate, the Bazett's is particularly not a good correction factor and the Fridericia's tends to be a very good correction factor. At the end of this month, we will have some comparisons of Fridericia's versus others.

When you get to the ISS phase, the integrated summary of safety in an application, you have the opportunity to actually look at all of the pretreatment ECGs that were obtained in the disease entity under consideration and you can calculate the correction factor that is useful for the population.

This was first done, from my experience, by neuropharm in the antipsychotic area where, in schizophrenics, they found that the correction formula of 0.37 was the best method for correcting the QT data in that particular disease entity.

What I am talking about is that the QTc equals the QT over the heart rate as measured by the RR interval raised to an exponential power. There are linear regression formulas and probably 30 other types of formulas.

Fridericia's is cubed root of the RR, or 0.33. If you use a population base, you might find it to be, as I just said for schizophrenics, 0.37 and for others it could be 0.28 or 0.41.

Finally, and most people in this field believe that you should take, in fact, individuals, every single individual in a clinical trial, and determine their correction formula and apply all

the ECGs for that individual by that individually defined correction formula.

To do that, you need 50 to 100 ECGs prior to therapy. The applications that are being discussed at the end of this month at Cardiorenal, in fact, did that. They had enough EKGs off therapy in their group that they were able to do individual-based correction formulas.

It is felt, of course, that this should be the most accurate, should be the most definitive, for a definitive Phase I trial. I think we will be seeing whether that, in fact, is true or whether one can use a simpler fixed formula.

[Slide.]

This is just the crowded figure that--what you are trying to do is this is as the heart rate slows, your QT interval on the Y axis increases. What you want to do is get this cloud to be as flat as possible with your correction formula.

[Slide.]

The final couple of slides are to talk about the statistical analysis that should be done with this data. There are lots of different possibilities, as you can imagine. In the November 2002 concept paper, there are a couple of pages

listed of everything that has been seen.

I must warn you that point-to-point analysis is very dangerous because if you only have one EKG at 10:00 a.m. and you think that is relevant to the 10:00 a.m. on drug because you think that is where Tmax is, that is okay to look at Tmax and Cmax. That makes common sense. But if you only have one EKG at each of those time points, of course you have lost your power to eliminate variability and, therefore, your degree of definitiveness obviously erodes.

So, central-tendency mean change, in my opinion, takes half the weight. You want to know what the mean change on the drug is compared--placebo-corrected to see if there is an effect or not an effect.

If your mean change is 0, you don't really have an effect, I, personally, have never seen an outlier that is necessarily correct, true, except in very unusual circumstances. So, if you do have some very small effect on the QTc, the cardiac repolarization, then, of course, the outlier analysis is half the weight or, in some people's opinion, three quarters of the weight because what you are really interested in is how many people are

going to be severely affected by the blockade of their HERG channel, if that is the mechanism.

Here, the principal categorical analyses--there are many you could do from normal to abnormal. Many of them are very sensitive. Many are maybe too specific. But these are the ones that I think are most relevant; maximum mean change to see what the maximum effect is any time, not just at Cmax because it may be a metabolite. There may be tissue penetration. 30 to 60 milliseconds is a fairly sensitive, maybe too sensitive, meaning a lot of people on placebo will have this effect.

Greater than 60 tends to be due to drug in most cases, particularly if you have adequate measurements, frequency and quality, but occasionally placebo patients may have this. How many people get new 500 milliseconds that are not having them at baseline or changes in their TU waves, another important analysis, to determine whether or not you have any abnormalities in morphology.

Don't expect to see or make an argument that because I didn't see torsades in my 3,000 patients that that means anything because the rate of torsades that one would see, even for a drug

like the terfenadine, was probably less than 1 in 100,000 so you need an awful lot of patients to say that you have excluded the possibility of clinical events.

[Slide.]

This is the current guidance from both Europe and the United States in terms of what the mean change, whether this is probably maximum mean change or Cmax change across the extent of the exposure is a little bit uncertain. Less than 5 milliseconds, everyone would agree, if you are in 0 to 5 millisecond mean central-tendency change, you can pretty much ignore that.

If you are over 20 milliseconds, you have got to have an awfully good argument to why you are thinking of putting this drug on the market because there is usually, in such drugs, a very high rate of torsades, at least the regulatory experience is such. Then, of course, anything between 5 and 20 is under a great deal of debate is to what the risk/benefit ratio is.

Most would say that 5 to 10 milliseconds for a drug that has reasonably strong benefit would be something of minimal concern, we still call it "not clear risk," where 10 to 20, everyone says, is

uncertain. Ziprasidone is an example of the drug with approximately a 14-millisecond or so effect that was put in the market because of its benefit/risk ratio.

[Slide.]

In the final slide, we will just summarize the overall cardiac safety analysis. It is not really totally defined by one trial although the new definitive Phase I trials that are being requested are, of course, going to be the one to look at the most. 076 in this case meets some of the these principles.

The preclinical data is something that is trumped by adequate clinical data, meaning if you have a HERG-positivity and you do a definitive trial and it is negative, it is now believed that one would ignore that preclinical data in terms of risk because in the targeted species, man, you have shown that the drug does not have this risk.

The thorough Phase I trial, as I said, is not only important to define the principal degree of cardiac risk but, of then, of course, one still needs to look at electrocardiograms in the target population in Phase II and Phase III but, if the Phase I definitive trial is negative, those ECGs

can be pretty routine. If it isn't, one needs to consider more intense monitoring in Phase II and III.

Finally, at the time of the ISS, one puts together all of the data and makes it relatively easy to come to a judgment.

Thank you very much for your attention.

DR. GULICK: Thanks, Dr. Morganroth.

Are there any quick questions from the committee for Dr. Morganroth?

Mr. Sharp?

MR. SHARP: I will just start off here. I just wondered if there are any other antiretroviral drugs that cause QT prolongation. I noticed the list of some of the prophylactic drugs. I was wondering about other antiviral drugs.

DR. MORGANROTH: I believe that ritonavir is known to prolong the QT. It is also a fairly, if not the most potent, blocker of 3A4, an enzyme that is used for the metabolism of many of these drugs. I am not an expert in the HIV area in terms of history with past drugs, so I don't know the regulatory history. Perhaps someone else on the committee could comment on that or maybe someone from the agency.

DR. GULICK: Dr. Birnkrant?

DR. BIRNKRANT: We periodically scan our postmarketing database for adverse events related to cardiac conduction, et cetera. It is an active process for us. So we are constantly looking for this type of signal. To date, basically, there are cases here and there but there is a lot of confounded data along with those cases. At this point, that is all I am prepared to say but we are actively looking for those types of signals.

DR. GULICK: Dr. Kumar.

DR. KUMAR: Could you comment on how, for the clinician, the places that we have seen problems with drugs known to prolong the QTc prolongation are patients who are on diuretics and then develop hypokalemia or hypermagnesemia. How can we assess that when clinical trials, most of these patients are usually healthy people who are not on diuretics or anything else that can prolong the QTc interval?

DR. MORGANROTH: If you are asking how can you assess whether a drug that you are using affects the QTc when you take care of a patient and you eliminate, for example, hypokalemia or other issues, the answer is, in my opinion, that you

can't very easily, can you, because you really need almost, like we discussed, a definitive trial that is very large, that is very controlled, that has a lot of ECGs before drug and on the drug. In a clinical setting, you don't really have that luxury because you hopefully may have an EKG before you started the drug and you might do an EKG for whatever reason on the drug, maybe, perhaps, to look to see if there is an effect.

But, in an individual patient, that is difficult to do. For example, in the oncology area, which is where this becomes relative, perhaps even in your area, when you have cytotoxic drugs and you can't do a controlled trial--you can't give it to normal volunteers and it is often difficult to use placebo in oncology patients. There, you have to do an outlier equivalent analysis.

That would be to see if there is a major change in the QTc duration. For example, 60 milliseconds would suggest that you are seeing a QTc effect. If your baseline was 400 and you are now 460, that might be an effect. You would want to sort of do a couple more ECGs to see if that doesn't go away quickly, within a few minutes, because it possibly could, if it is just

variability.

So it is difficult, without doing a definitive trial, to be certain. A 60-millisecond effect, a new 500-millisecond effect, would be what you would be concerned about. So anything over 500, you would be very concerned or 60 milliseconds, you might consider a drug, would be the best answer.

DR. GULICK: Yes?

DR. KOWEY: Can I just respond to the other question about other antiviral drugs? Almost all the protease inhibitors do have an effect on IKr. I don't think that we have--as Joel was intimating, I don't think we have the kind of clinical-trial data that would tell us how much of that translates into a QT-prolonging effect.

But I would be surprised if the other protease inhibitors didn't have this effect based on the relative potency of their effect on IKr. In fact, the drug we are looking at today is probably one of the weakest of the IKr blockers within this family of agents.

So I think it is probably a yes to your question.

DR. GULICK: Okay. Thanks for that. Just

to remind the committee, we are going to have lots of time to get into this later. I will take one last question from Dr. Wood.

DR. WOOD: I was just wondering if you could comment on QT intervals in the pediatric population, if there are any changes developmentally?

DR. MORGANROTH: The pediatric population, in my experience, has been obviously insufficiently studied in general and particularly for the QT issues of drugs. I have seen two or three trials attempting to do this in pediatrics and I don't have sufficient data to really give you any generalizations or comments. But it is perfectly reasonable and easy to do. Of course, EKGs are noninvasive. You can do them.

I think as more pediatric trials are done and more intense concern about safety issues in children are raised with this we will be able to get the data. Right now, it is just an area that has, in my opinion, sufficient data to know how one can translate adult findings into pediatrics. It is assumed to be the same.

DR. GULICK: Thank you, Dr. Morganroth.

Just to remind everyone, we will have lots

of time to go into more details and Dr. Morganroth is on the committee today so we can seek his advice later.

Two additional members joined the table, so please introduce yourselves and state your affiliations. Dr. Sherman and Dr. Goldberger.

DR. SHERMAN: Ken Sherman, University of Cincinnati.

DR. GOLDBERGER: Mark Goldberger from the Office of Drug Evaluation IV at FDA.

DR. GULICK: Thank you.

We will turn now to the sponsor presentation from Bristol-Myers Squibb.

Sponsor Presentation - Bristol-Myers Squibb

DR. SIGAL: Good morning.

[Slide.]

My name is Elliott Sigal. I am Head of Development for Bristol-Myers Squibb. I would like to thank the committee for this opportunity to describe our clinical studies on atazanavir.

In the early 80's, when physicians were first seeing patients with what was later named AIDS, I don't think they ever would have imagined we would be here today discussing the challenges and opportunities that have arisen because of the

chronic nature of HIV therapy.

As patients live longer, drug therapies need to have new resistance patterns, better side-effect profiles and dosing that supports extended use. Because of these challenges, HIV AIDS remains a disease for which new and improved therapies are important.

[Slide.]

Atazanavir is a new addition to our armamentarium for the treatment of this disease and for meeting these challenges. It has a distinct resistance profile. Resistance is infrequent but, as you will see, we have characterized a signature mutation that we believe has opportunity for preserving future treatment options.

Unlike other protease inhibitors, atazanavir has far less effect on cholesterol and triglyceride levels. Its favorable lipid profile potentially reduces the need for concomitant medicines. Finally, atazanavir offers once-daily dosing which reduces, importantly, the pill burden for these patients.

These attributes, along with an acceptable safety tolerability profile and demonstrated efficacy, address what we see today as important

medical needs. We designed atazanavir's development program to establish its ability to meet these needs.

[Slide.]

A substantial clinical program with over 2500 subjects studied and 1500 patients treated with atazanavir has demonstrated the efficacy and safety of atazanavir. This program has studied a wide variety of HIV-infected individuals including treatment-naive, treatment-experienced and pediatric patients.

Studies have demonstrated efficacy extending past two years. In addition to the Phase II and Phase III trials, patients have received atazanavir through an early-access program. As you heard, part of the process of bringing a novel therapy into treatment is the characterization of its safety profile and to do so comprehensively.

As part of BMS's ongoing safety program, we have worked to examine any effects on cardiac electrophysiology. In addition, we have examined and characterized the effects of bilirubin. We have then worked extensively with the FDA and our experts to determine the implications of these results.

To further explore these findings today, we have arranged to have available to you outside experts to respond to any questions and supplements to our company presentation. Our list of experts is on the following two slides.

[Slide.]

They are available to you and prepared to comment on specialty areas of HIV resistance, lipid levels in HIV infection, cardiac electrophysiology issues.

[Slide.]

HIV clinical paradigms and hyperbilirubinemia.

[Slide.]

Based on our program, we are seeking an indication for the treatment of HIV in combination with other antiretroviral agents for the treatment of HIV infection. This indication has evolved through our discussions with the agency.

[Slide.]

The presentation of the clinical program will begin with Dr. Steve Schnittman. Steve will describe the clinical-development program and clinical-trial results.

Because of the evolving norm, as you

heard, to extensively characterize the electrophysiology effects of all new chemical entities, Dr. Jack Lawrence, one of our cardiologists, will speak to these issues. You will hear our conclusion that we think atazanavir has no significant effect on QT interval.

Dr. Michael Giordano will describe the drug's effect on bilirubin and characterize its lipid profile. I will then return to present a brief summary of benefit/risk.

Dr. Schnittman?

Clinical Development Program and Clinical Trial Results

DR. SCHNITTMAN: Thank you, Elliott, and good morning everyone.

[Slide.]

My role today is to present the atazanavir clinical-trial program and show how the program supports the safe and efficacious use of atazanavir in a diverse HIV-infected patient population. First, the intrinsic properties of atazanavir will be described including ADME features, a summary of drug-drug interactions, and early findings in the program that guided dose selection for Phase III clinical trials.

The bulk of the presentation will be clinical-trial results. Study findings in the antiretroviral treatment-naive patient population will be described including information regarding overall viral susceptibility and the distinct resistance profile for atazanavir that is emerging.

Next, we will review the data in treatment-experienced patients. These patients face problems with emerging HIV resistance and treatment-associated comorbidities, and we will be presenting data from two trials in diverse experienced-patient populations.

Before presenting the pivotal clinical studies, let's briefly review the ADME which provided critical information to guide clinical-study design and the drug-drug interaction profile that is essential for the proper and safe use of atazanavir.

[Slide.]

Atazanavir is rapidly absorbed. Food increases atazanavir exposure and decreases the intersubject variability. Therefore, atazanavir should be administered with food. Atazanavir protein binding of 86 percent is in the mid-range for PIs. Atazanavir is primarily metabolized in

the liver. It is a substrate and a moderate inhibitor of CYP3A4 with a Ki in the mid-range of PIs.

Thus, atazanavir may have the potential to alter the clearance of drugs that are metabolized by CYP3A4. Furthermore, atazanavir may have its metabolic clearance altered by drugs that have the potential to inhibit or induce CPY3A4.

These characteristics of atazanavir metabolism drove the drug-drug interaction program and provided guidance for the safe and efficacious use of concomitantly administered medicines.

While not metabolized by the enzyme, atazanavir is also a competitive inhibitor of UGT 1A1, like indinavir, but quantitatively more significant. This inhibition of bilirubin glucuronidation was a consideration in our dose selection.

Finally, atazanavir is primarily eliminated in the feces with minimal urinary excretion and has an elimination half-life of about seven hours.

[Slide.]

The drug-drug interaction profile for atazanavir was evaluated in a series of clinical-

pharmacology studies. The entire program is in your briefing document in Appendix 1 beginning on Page 214. But summarized here are the complete recommendations.

This evaluation included drugs that are commonly taken by HIV-infected patients. No modification in dosing for atazanavir or coadministered drug was noted in many cases. There are certain drug-drug interactions that have potentially important PK or PD effects because of CYP3A4 interactions.

These include drugs whose dosing should be modified due to atazanavir's inhibition of CYP3A4 including saquinavir, clarithromycin, rifabutin, diltiazem and oral contraceptives. Some of these will be further described in the Special Topics part of the presentation.

Other drugs require atazanavir dosing modifications because of either CYP3A4 induction, as seen with efavirenz, or with CYP3A4 inhibition as seen with ritonavir. Finally, atazanavir should be separated in dosing from buffer formulation ddI and, although not studied, this may be expected to apply to antacids in general.

[Slide.]

To select the dose for the Phase III studies in treatment-naive patients, a combination of pharmacokinetic and pharmacodynamic data was analyzed, integrated and assessed. This single figure sums up our overall rationale for dose selection. It displays the steady-state concentration curve over a twenty-four hour dosing period in the fed state for atazanavir at 400 milligrams.

The Cmin or trough at the far end of the curve is the PK parameter that best correlates with antiviral activity of atazanavir, and this is true for protease inhibitors as a class. For atazanavir 400 milligrams once a day, the trough in patients is a mean of about 150 nanograms per ml.

In addition, we provide the estimated protein-adjusted EC90s for atazanavir as a cluster of dots. These data were determined from 93 consecutive antiretroviral-naive subjects who were randomized to this study. Given the median estimated protein-adjusted EC90 of 14 nanograms per ml, the ratio of mean Cmin to adjusted EC90 is in excess of 10.

This provides a PK cushion throughout the dosing period for the range of virus

susceptibilities encountered in a naive patient population. Other PK and PD assessments, as well as safety and efficacy evaluations, in the large dose-ranging Phase II clinical studies 007 and 008 further support the dose selection of atazanavir 400 QD for treatment-naive patients. This is consistent with the accepted convention of HIV therapeutics that one should pick the highest tolerable dose.

[Slide.]

Two weeks of atazanavir monotherapy demonstrated a dose-related mean RNA decline. This is consistent with hollow-fiber in vitro modeling demonstrating the adequacy of doses of 400 milligrams QD or greater.

The Phase II studies also demonstrated a nonlinear dose relationship to Cmin with a large increase in trough level from 200 to 400 milligrams and much smaller increases in the trough with doses above 400 milligrams. Importantly, the Cmins for 200 milligrams were inadequate relative to the median EC90 in naive patients.

[Slide.]

Elevations in bilirubin are dose-related, best correlate with Cmin and doses of 500 and 600

milligrams were associated with significantly greater elevations in bilirubin of at least five times the upper limit of normal and did not appear to offer additional efficacy.

[Slide.]

Confirmation of the efficacy of the 400-milligram dose of atazanavir as compared to nelfinavir was demonstrated by the solid virologic response over 48 weeks from the two large Phase II studies 007 and 008. The 400-milligram once-daily dose provided the best balance of maximizing antiviral efficacy while minimizing the risk of potential adverse events.

[Slide.]

Therefore, atazanavir 400 milligrams was chosen as the optimal dose to be evaluated in Phase III studies in treatment-naive patients. I will now provide the results of Study 034, the pivotal Phase III study in antiretroviral-naive subjects.

[Slide.]

034 was an 810-subject, double-blind, double-dummy active controlled multinational study that randomized subjects to either atazanavir 400 once daily or efavirenz 600 once daily. Subjects on both arms received zidovudine plus 3TC BID as a

fixed-dose combination.

Please note, nucleoside changes were not permitted in the study. Efavirenz was the selected comparator as it is the standard of care in treatment-naive patients.

[Slide.]

The baseline characteristics of the subjects enrolled in Study 034 were well balanced overall. Of interest, more than one-third of the subjects enrolled were female. Two thirds were non-white. The median HIV RNA was 4.9 logs with over 40 percent of subjects having greater than 100,000 copies HIV RNA.

Of note, retention was high with 82 percent of subjects remaining on study through Week 48. The similarity of virologic efficacy between the atazanavir and efavirenz regimens is demonstrated in the next slide.

[Slide.]

The primary endpoint for the study was the virologic response through 48 weeks which is the proportion of subjects below 400 copies per ml RNA. This is an intent-to-treat analysis, non-completers equal failure, based on the most recent FDA-proposed algorithm for virologic response. The

figure demonstrates that both treatment regimens are highly active.

[Slide.]

The primary analysis, virologic response, below 400 copies through 48 weeks, atazanavir, shown in green, was similar to the efavirenz regimen and statistically noninferior. The response rates were 70 percent and 64 percent respectively.

For the secondary endpoint of virologic response through 48 weeks for LOQ50, the response rates were 32 percent and 37 percent respectively and they also met the criteria for similarity. These data demonstrate the durable efficacy of the 400-milligram, once-daily, dose of atazanavir in antiretroviral-treatment-naive patients relative to a widely accepted standard of care.

Subpopulation analyses for the principal efficacy parameters confirm consistent between-treatment comparisons based on gender, race, region and HIV RNA level. For subjects with baseline RNA less than 100,000, virologic responses were comparable between treatment regimens, as seen on the left, and this comparability was also seen for treatment regimens for subjects with baseline RNA

greater than 100,000, seen on the right.

[Slide.]

In order to understand the development of resistance in naive patients with virologic failure, phenotypic and genotypic determinations were performed by Virologics and LabCore respectively. Samples from patients with protocol-defined virologic failure in Study 034 and who had viral loads of greater than 1,000 copies per ml were assayed.

Resistance develops infrequently in atazanavir patients meeting the protocol definition of virologic failure. Working down the column, 26 of 69 atazanavir virologic-failure patients were able to be pheno- and genotyped. Of these 26, only 6 demonstrated decreased susceptibility to atazanavir--i.e., greater than 2.5 times the control, EC50. Notably, all six of these isolates had the I50L substitution.

In addition, the only genotypic changes consistently seen in isolates from patients experiencing virologic failure in antiretroviral naive studies has been the I50L substitution. Across the naive-patient studies, decreased susceptibility to atazanavir occurs infrequently,

being observed in 2 percent of all subjects and about 11 percent of atazanavir treatment failures.

[Slide.]

In PI treatment-naive subjects who develop virologic failure in Phase II and III studies, 23 on-study resistant isolates have been assessed and all have the I50L signature mutation. Furthermore, each of these I50L-containing isolates demonstrates atazanavir-specific resistance with decreased viral fitness and maintained or enhanced susceptibility to all other PIs tested.

These features of the I50L genotype are promising with respect to preserving the PI class and preserving future treatment options.

[Slide.]

We also looked at CD4 cell counts as a marker for immunologic response in O34. CD4 cells increase substantially and throughout the study duration. The mean increase at Week 48 was 176 cells on the atazanavir-containing regimen, 160 cells on the efavirenz-containing regimen, each of which contained ZDV 3TC.

These data support the durable efficacy of atazanavir 400 relative to a potent standard of care.

[Slide.]

The safety and tolerability of atazanavir was also carefully assessed. Adverse events seen in the 034 study are presented in the slide and demonstrate the overall safety and tolerability profile of atazanavir. Rash and dizziness were more common on the efavirenz regimen whereas jaundice and scleral icterus were more frequent on the atazanavir regimen. The jaundice and scleral icterus were not associated with hepatotoxicity and reflected benign elevations in unconjugated bilirubin.

This will be addressed in detail by Dr. Giordano.

[Slide.]

The ability of heart regimens to provide durable efficacy and safety to patients is of paramount importance. To this end, the atazanavir program has continued long-term dosing and monitoring of patients in order to provide this information.

One such study is the 008/044 Phase II rollover. Subjects who were enrolled in the 008 dose-ranging study and who had successfully completed the trial and were virologically stable

were eligible to enter this extended dosing phase and to continue in one of three arms, either atazanavir 400 on the left, atazanavir 600 in the middle, or switch from nelfinavir to atazanavir 400 each in combination with continued d4T/3TC.

[Slide.]

The cohort of subjects on atazanavir 400 that enrolled in 044 received a median cumulative treatment of about 109 weeks. The virologic response was sustained and durable for subjects treated with atazanavir 400, shown in green, 82 percent for LOQ 400, 50 percent for LOQ 50 and was comparable to patients treated with atazanavir 600, shown in blue. Of note, virologic suppression was maintained for those who switched from nelfinavir to atazanavir 400.

These long-term extension results support the durable efficacy of atazanavir 400.

[Slide.]

These same patients have also demonstrated continued immunologic responses over time. We observed substantial CD4-count increases of about 350 cells for the atazanavir 400-milligram arm beyond two years further supporting the sustained efficacy of this dosing regimen.

We conclude from studies in antiretroviral treatment-naive subjects the following.

[Slide.]

In a large adequate and well-controlled Phase III study, the 400-milligram dose of atazanavir has been shown to be safe and highly efficacious over 48 weeks relative to the non-nuc efavirenz. These findings are supported by those in two large Phase II studies in which atazanavir was shown to be safe and as efficacious as the PI, nelfinavir.

Furthermore, the extended follow up of patients in the Phase II studies supports the durable efficacy and safety beyond three years of dosing with atazanavir 400. Resistance to atazanavir develops infrequently in treatment-naive patients and, when it does, the I50L signature mutation consistently appears which may preserve future therapeutic options.

[Slide.]

In addition, and to be presented by Dr. Giordano, atazanavir demonstrates no increase in cholesterol and triglycerides with less need for lipid-lowering agents.

[Slide.]

Having demonstrated safety and efficacy in antiretroviral-naive patients, let's turn our attention to the experienced patients. We will begin with the rationale for dose selection and then the clinical data in support of the safety and efficacy of atazanavir in these patients.

[Slide.]

Treatment-experienced patients are heterogeneous for several reasons. These patients have been exposed to a variety of combination therapies and for varying periods of time. The virus in these patients generally has decreased antiretroviral susceptibility with a variety of mutations.

Several strategies were explored; atazanavir, 400 milligrams unboosted, atazanavir boosted with ritonavir and atazanavir combined with a second PI with a nonoverlapping resistance profile. In current clinical practice, most PIs are boosted with ritonavir in order to enhance PK.

However, there are features of the atazanavir profile that prompted our looking at unboosted atazanavir in experienced patients.

[Slide.]

The strategy for unboosted atazanavir 400

in treatment-experienced patients who only failed a single PI was based on the fact that atazanavir susceptibility was maintained in 86 percent of viral isolates resistant to one or two PIs. In addition, we determined the 400-milligram once-daily dose mean trough level of 150 was significantly above the EC90s of many of these experienced patient virus isolates.

Together, this information supported the trial of an unboosted 400-milligram atazanavir dose as a single PI for a Phase III study in patients who previously failed a single PI. This is the 043 study.

[Slide.]

Such patients were randomized to receive either atazanavir at 400 once daily unboosted or lopinavir boosted with ritonavir twice daily. Lopinavir/ritonavir was the selected comparator as it is the standard of care in treatment-experienced patients.

Each of these dosing regimens was combined with two nucs to which the patient was phenotypically sensitive. Of note, one-third of the subjects selected D4T ddI and one-third of subjects selected abacavir plus a second nuc. 300

subjects were randomized and, as per the protocol-plan primary analysis, and as per FDA agreement, the first 229 subjects are included as the lead cohort through 24 weeks while safety data is included for all subjects.

For our purposes today, all efficacy analyses presented by us will reflect the lead cohort. We, in the FDA, have subsequently analyzed the safety and efficacy on all patients through 24 weeks and it is these latter analyses that will be presented by the FDA today.

[Slide.]

Overall, the baseline characteristics for the subjects enrolled in this study were well balanced. About 20 percent of subjects were female. More than half were nonwhite. Approximately 28 percent of subjects had a prior AIDS-defining diagnosis.

[Slide.]

Patients in 043 did have a moderate amount of prior experience with antiretroviral agents. This included prior history of 140-week mean exposure to protease inhibitors, 180 weeks to nucs, and 85 weeks to non-nuc RT inhibitors.

[Slide.]

The patients prior PI exposure is reflected in this phenotypic sensitivity pattern. More than half the patients had decreased susceptibility to nelfinavir. The majority were fully susceptible to atazanavir and lopinavir, IC50 less than 2.5 times control.

[Slide.]

The HIV RNA mean change from baseline, expressed as a time-average difference, was a coprimary endpoint in the 043 study. Over the first few weeks, a very rapid RNA decline in both treatment arms of approximately 1.5 logs is noted. That decline then stabilizes for unboosted atazanavir while, in contrast, there is further RNA decline on the boosted lopinavir/ritonavir arm.

The difference between these regimens, in terms of time-average difference, was approximately 0.31 logs through 24 weeks that favored lopinavir/ritonavir and was significant.

It is not unexpected that the unboosted atazanavir regimen was less efficacious than the lopinavir/ritonavir boosted regimen. The reduction from baseline in HIV RNA was substantial for atazanavir. It is therefore important to determine the contribution of the atazanavir component of the

regimen to the regimen's efficacy.

This was estimated by retrospective comparison to results from studies evaluating dual-nuc regimens.

[Slide.]

Five historical controls were identified. They were conducted in treatment-experienced populations. They contained at least one treatment group with only dual-nuc therapy and that reported analyses of RNA at baseline and Week 24. Estimates of the Week 24 RNA change from baseline for dual-nuc treatment arms ranged from -0.25 to -0.89 log.

A combined estimate representing the dual-nuc treatment effect is -0.64 log with a tight 95 percent confidence interval seen in the top orange bar.

In 043, the Week 24 mean RNA change from baseline for atazanavir combined with dual-nuc therapy was -1.73 log. Note that the atazanavir confidence interval, shown in green, does not overlap the confidence interval for the individual or combined estimates for dual nucs.

We conclude that the atazanavir regimen has significantly greater RNA decline as compared with the dual-nuc therapy alone. Despite the

inherent biases of historical and cross-study comparisons, the large difference observed between atazanavir with two nucs and two nucs alone overcomes many of these limitations. Therefore, atazanavir contributes to the efficacy in the treatment-experienced population beyond what would be expected with dual-nucs alone.

[Slide.]

Now let us compare the virologic responses for the unboosted atazanavir and the boosted lopinavir/ritonavir arms based upon the proportion of subjects below HIV RNA limit of quantitation which was a secondary endpoint. Through 24 weeks, antiviral efficacy was demonstrated for the boosted lopinavir/ritonavir regimen with 81 percent below LOQ 400 and 52 percent below LOQ 50.

Substantial efficacy was also demonstrated for the unboosted atazanavir regimen with 61 percent below 400 LOQ and 41 percent below LOQ 50. It is not surprising that the boosted PI performed better than a nonboosted PI. With efficacy of the atazanavir 400 having been demonstrated in the experienced-patient population, exploratory analyses were performed. While these exploratory analyses do not explain the differential efficacy

observed between boosted and nonboosted PIs, they do suggest phenotypic and genotypic parameters at baseline that may be predictive of a good virologic response for atazanavir.

[Slide.]

Better virologic responses to atazanavir were determined for the following subgroups; subjects having no demonstrable phenotypic resistance to atazanavir--i.e., less than 2.5 IC50 control--and subjects having been exposed to only one prior PI regardless of baseline nuc mutations.

As seen in this table, virologic response rates for atazanavir in these subgroups were enhanced up to 68 percent for LOQ 400. Therefore, a clinician may conclude that atazanavir, at 400 milligrams unboosted, would be most appropriate in experienced patients with minimal evidence of resistance, a patient profile that is commonly seen in early PI failures.

[Slide.]

With respect to immunologic response, significant improvement in CD4 cell counts were seen and continued to rise over 24 weeks. The mean increase at Week 24 was 101 cells on the atazanavir-containing regimen and 121 cells on the

lopinavir/ritonavir-containing regimen. The improved immunologic parameters support the efficacy contribution of atazanavir.

[Slide.]

It is important to note that the coprimary endpoint for the study was a comparison of the mean percent change in fasting LDL cholesterol from baseline between the two arms at 24 weeks. In this figure, we see a notable rise in LDL cholesterol on the lopinavir/ritonavir regimen with a decline on the atazanavir regimen that was significantly different per-protocol-defined objective.

This is just one of multiple studies that confirm the unique lipid profile of atazanavir and which will be expanded upon later.

[Slide.]

Let's move on to safety assessments. Adverse events seen in the 043 study are presented here and demonstrate the overall good safety and tolerability of atazanavir in this population. There was more diarrhea and nausea on lopinavir/ritonavir but more jaundice on atazanavir. The jaundice was not associated with hepatotoxicity and reflected benign elevations in unconjugated bilirubin and will be addressed in

detail by Dr. Giordano.

[Slide.]

We conclude from the 043 study that atazanavir 400 has demonstrable safety and efficacy in the treatment-experienced population. The majority of patients are able to achieve LOQ 400 with the best responses seen in patients without evidence of phenotypic resistance to atazanavir having been exposed to only one prior PI, irrespective of baseline nuc mutations.

A superior lipid profile was demonstrated for atazanavir relative to lopinavir/ritonavir. Therefore, atazanavir efficacy was associated with a substantial lipid benefit and thus represents an important treatment option for experienced patients.

[Slide.]

As we have previously stated, the experienced patient population is heterogeneous, while we have identified where atazanavir has substantial efficacy, we realize that the more highly treatment-experienced population might benefit from alternative dosing approaches.

[Slide.]

This group of patients is characterized by

extensive use of prior PIs and nucs with associated geno- and phenotypic resistance. For these highly experienced patients, BMS has evaluated two different dosing strategies. One is the boosting of atazanavir with ritonavir in order to provide a more robust atazanavir PK profile.

The second is combining atazanavir with another PI with nonoverlapping resistance, specifically saquinavir.

[Slide.]

We know patients with prior exposure to PIs may require higher drug levels to suppress virus because of decreased susceptibility to both the PI and nuc components of HAART. In this figure, the PK profile of atazanavir in healthy volunteers, given as a 300-milligram once-daily dose in combination with 100-milligram once-daily dose of ritonavir is shown in blue and, for illustrative purposes, it is compared to a typical concentration curve for atazanavir 400 once-daily, also in healthy volunteers, shown in green.

In addition, we provide the estimated protein-adjusted EC90s for atazanavir as a cluster of dots determined from all subjects in the multiple-treatment-failure 045, Note the broad

range of reduced susceptibilities. Ritonavir primarily slows the elimination phase of atazanavir. You see a substantial increase in exposure, two- to three-fold, and a trough on the order of 5- to 8-fold, with the boosted atazanavir.

In addition, there is a decline in variability of drug concentrations in the presence of ritonavir. Furthermore, the Cmax which may be expected to drive certain adverse events of drug but not bilirubin elevations was very similar for atazanavir boosted and unboosted.

In other PK studies, doses of atazanavir and ritonavir greater than 300 and 100, respectively, indicated a concern of increased adverse effects due to higher peaks and troughs. In fact, two studies in healthy volunteers have demonstrated that atazanavir 300 combined with ritonavir 100 once daily provide an optimal PK/PD and safety profile supporting its selection for a Phase III study in patients who failed multiple HAART regimens, Study 045.

[Slide.]

In Study 045, patients were enrolled who failed at least two HAART regimens that included an antiretroviral from each therapeutic class. These

highly treatment-experienced patients were randomized among three arms. For the first two weeks, they maintained their nuc backbone and replaced their PI or NNRTI with one of the following; combination of atazanavir 300 with ritonavir 100 once daily on the left, combination of atazanavir 400 with saquinavir 1200 once daily in the middle, or lopinavir 400 with ritonavir 100 given BID on the right.

From Week 2 onward, the NNRTI backbone was replaced with tenofovir 300 once daily plus a nuc to which the patient demonstrated phenotypic susceptibility.

The FDA has reviewed the interim analysis for efficacy that includes 106 of 358 subjects through Week 16 and for safety on all subjects through Week 16. However, we will briefly provide an updated analysis that includes the efficacy on all subjects through 24 weeks, an analysis you also find within the briefing document.

For consistency, all future displays for Study 045 will include the 24-week unreviewed data. Of interest, 35 percent of the subjects in 045 had a prior AIDS diagnosis and these patients, indeed, were heavily treatment-experienced with about five-and-a-

half years of prior antiretroviral use.

The relative efficacy of the various dosing strategies is demonstrated on the next slide.

[Slide.]

The HIV RNA mean change from baseline expressed as a time-average difference is the primary endpoint. All three regimens show similar rapid declines in RNA of about 1.25 log over the first two weeks during which time only the PI was switched. Through Week 24, there is approximately 1.52 log RNA decline in the atazanavir/saquinavir arm, 1.86 log decline in the atazanavir 300 ritonavir-boosted arm, and 1.89 log decline in the lopinavir/ritonavir-boosted arm.

In terms of the time-average difference, there were no significant differences in efficacy between atazanavir/ritonavir and lopinavir/ritonavir regimens while lopinavir/ritonavir regimen was more efficacious than atazanavir/saquinavir.

[Slide.]

This table summarizes the virologic response as the proportion of subjects with HIV RNA below limit of quantitation either 400 or 50. For

the treatment regimens at 24 weeks as intent-to-treat analyses, these data demonstrate that the atazanavir 300 ritonavir and lopinavir/ritonavir-containing regimens showed solid and comparable efficacy through 24 weeks, 64 percent and 62 percent, respectively for LOQ 400.

This is in contrast to the atazanavir/saquinavir arm which had a substantial but lower response rate of 44 percent. In addition, the proportion of subjects with virologic response rates for LOQ 50 was comparable for atazanavir/ritonavir and lopinavir/ritonavir regimens.

[Slide.]

The longitudinal virologic response rates over 24 weeks for the two boosted regimens are displayed in this figure as well for both the LOQ 400 and LOQ 50. These data confirm the similarity of the atazanavir/ritonavir, shown in green and lopinavir/ritonavir shown in orange to these highly treatment-experienced subjects.

With respect to immunologic response, we see substantial improvement in CD4 counts over the 24 weeks with a similar rise of 83 and 90 cells on atazanavir/ritonavir and lopinavir/ritonavir arms.

These were somewhat higher than the cell-count rise on atazanavir/saquinavir.

These increases are highly substantial for the treatment-experienced patient population and are of the magnitude known to confer clinical benefit. Safety assessments in 045 demonstrated that atazanavir has a safety and tolerability profile in these highly treatment-experienced patients that is similar to that seen in naive patients.

[Slide.]

Working across the columns, jaundice and scleral icterus were observed for 6 percent and 3 percent of subjects respectively on the atazanavir/ritonavir arm. Atazanavir/saquinavir subjects experienced more GI intolerance, nausea and vomiting, which contributed to the higher discontinuation rate relative to the two other arms.

In contract, the lopinavir/ritonavir arm experienced predominantly diarrhea as an adverse event, 11 percent.

[Slide.]

We conclude from the 045 study in highly treatment-experienced patients that, through 24

weeks in unreviewed data, atazanavir 300 boosted with ritonavir demonstrates efficacy that is comparable to lopinavir/ritonavir. Atazanavir/ritonavir provides a good safety and tolerability profile and the preference for a ritonavir boosting strategy for atazanavir in highly experienced patients is becoming clearer.

[Slide.]

We conclude from these pivotal and supporting clinical studies that the efficacy of atazanavir has been confirmed to be similar to both efavirenz and nelfinavir in treatment-naive patients at the 400-milligram once-daily dose. Extended studies in naive patients demonstrated durability of treatment effect to at least 108 weeks.

We have also demonstrated the efficacy of the 400-milligram dose in treatment-experienced patients. Resistance develops infrequently in atazanavir-treated patients but, when atazanavir resistance does develop in naive and susceptible experienced patients, one sees a unique signature mutation, the I50L, which may preserve future treatment with PIs.

We have demonstrated that atazanavir is

safe and well tolerated at the 400-milligram once-daily dose in both treatment-naive and experienced patients.

Two points will be discussed in upcoming presentations. First, hyperbilirubinemia and jaundice are dose-related adverse events that are manageable and are not associated with hepatotoxicity. Second, atazanavir has a consistent, durable lipid profile that may provide reduced cardiovascular risk.

Drug-drug interactions have been well characterized including diverse antiretroviral combinations that have been shown to be safe and other concomitant drugs for which PK/PD impact have been assessed. These latter interactions will be further addressed by Dr. Lawrence. Finally, early data from 045 demonstrates the utility of ritonavir boosting of atazanavir for treatment-experienced patients. More data will be forthcoming from 045 and other studies to fully characterize atazanavir-boosting strategies.

We will now turn to considerations that arose during the atazanavir development program. These include cardiac electrophysiology evaluations, hyperbilirubinemia and the very

positive and unique lipid profile of atazanavir.

Dr. Jack Lawrence will now present the cardiac-electrophysiology profile.

Cardiac Electrophysiology Evaluations

DR. LAWRENCE: Thank you, Steve.

[Slide.]

The development program for atazanavir included extensive assessments of the potential for atazanavir to affect cardiac electrophysiology.

[Slide.]

Our assessment included the following elements. Preclinical studies suggesting that atazanavir was comparable to other protease inhibitors with respect to potential to prolong the QTc interval, and assessments of QTc and PR intervals in human studies including 8 studies in 254 healthy volunteers.

There were also 5 clinical studies including 1,037 HIV-infected patients taking atazanavir and 629 patients taking comparator drugs.

These studies demonstrated that atazanavir is comparable to other HIV drugs in terms of clinical cardiac electrophysiology.

[Slide.]

We have examined the electrophysiological effects of atazanavir in several in vitro and in vivo studies. We studied specific ion channels that play important roles in cardiac conduction and repolarization. HERG and Purkinje studies are important for identifying drugs with the potential to cause clinical effects on the QT interval.

Atazanavir blocks sodium and HERG potassium channels with IC50s greater than 30 micromolar and blocks calcium channels with an IC50 of about 10 micromolar. To put these results into perspective, these effects are modest and all protease inhibitors we tested blocked HERG or prolonged action potential duration with in vitro potency similar to or greater than atazanavir.

In a 9-month in vivo toxicology study in dogs, and up to 7-fold the human exposure by AUC, there were no electrocardiographic changes. Although we detected a weak in vitro signal, we saw no QT changes in dogs or subsequently in human studies.

[Slide.]

The 076 study was a double-blind, placebo-controlled, crossover study designed to evaluate the effects of atazanavir on the QTc and PR

intervals. Seventy-two subjects received three treatments - placebo, 400 mg atazanavir and 800 mg atazanavir in a randomized sequence, each treatment for six days with at least a 14-day washout period between treatments.

Serial electrocardiograms, 11 per 24 hours, were collected the day prior to dosing and at steady-state on Day 6 of each treatment period, along with PK samples on Day 6.

The primary endpoints for this study were based on the QTc and PR intervals and their changes from baseline on Day 6.

This study was the focus of our healthy volunteer assessment of QTc changes and included evaluations of heart rate and the PR interval.

As described by Dr. Morganroth, the QT interval is a marker for drug effects on cardiac repolarization. Because the QT interval varies inversely with heart rate, a variety of heart rate correction formulas have been developed. Bazett's formula and Fridericia's formula are the most widely used.

Consistent with the current FDA draft guidance on QTc, we were encouraged by the Antiviral Division to analyze our QT data using

Fridericia's formula in addition to analyses we had initially submitted using Bazett's formula.

In the 076 study, we observed a 3 beat per minute mean increase in heart rate at the 400 mg dose, and an 8 beat per minute mean increase in heart rate at the 800 mg dose. Changes of this magnitude especially at the 800 mg dose have the potential to result in overcorrection of QT intervals to prolonged values of QTc using Bazett's formula, but not using Fridericia's formula.

Our assessment of QTc included the mean changes from baseline, the number of individual subjects with prolonged QTc, and the concentration dependence of QTc changes. We will review data using both Fridericia's and Bazett's formulas. Our initial analysis of the 076 study suggested a subclinical signal for Bazett-corrected QT prolongation.

[Slide.]

Using Bazett's formula, regression analyses suggested a small concentration-dependent effect of atazanavir on QTc. Looking at changes in QTc using the average value, the maximum value, or the value at Tmax, the changes in mean QTc at 400 mg were smaller than placebo, and at 800 mg, were

greater than placebo. No subject had a QTc greater than 500 milliseconds.

On placebo, one subject had a change in QTc greater than 60 milliseconds, and on 800 mg, three subjects had a change greater than 60 milliseconds, a potentially clinically important level of change. All four of these subjects had time-matched increases in heart rate of 20 beats per minute or more, suggesting that the tendency for Bazett's formula to overcorrect at increased heart rates caused these to be false positive elevations.

When we performed the same analyses using Fridericia's formula, which is a more appropriate correction formula in subjects with altered heart rates, we saw no effect of atazanavir on QTc.

[Slide.]

This is reflected in the scatterplot of QTc Fridericia versus the plasma concentration of atazanavir for which regression analyses showed no concentration-dependent effect on QTc. The placebo range of QTc at zero concentration encompassed all on-treatment values of QTc, further suggesting a lack of atazanavir effect.

By the same measures of change in QTc

described on the previous slide, mean changes in QTc at 400 mg and at 800 mg were less than placebo. Furthermore, no subject had a QTc greater than 500 milliseconds or a change greater than 60 milliseconds.

We also measured QT intervals in four studies with active comparators.

[Slide.]

The comparators were nelfinavir, efavirenz, and lopinavir/ritonavir. These data demonstrated a low frequency of prolonged QTcF comparable for atazanavir and the comparators. There were no prolongations greater than 500 milliseconds, no effect on gender was apparent. Overall, atazanavir was comparable to other HIV drugs with respects to changes in QTc and had no clinically significant effects on cardiac repolarization.

[Slide.]

In summary, there was no concentration-dependent effect of atazanavir on QTcF. There were no individual subjects with outlier values of QTcF, and the frequencies of prolongation in QTc were comparable between atazanavir and comparators. Overall, the data demonstrate that atazanavir has

no clinically significant effect on QTc.

During the course of the evaluation of potential effect on repolarization, we did observe dose-dependent prolongation of the PR interval.

[Slide.]

The PR interval represents the conduction time from the atrium to the ventricle. An AV block is a delay or an interruption of conduction that can occur with different gradations.

First-degree AV block, defined as an increase in the PR interval to greater than 200 milliseconds, is really just conduction delay without block. It is almost always asymptomatic and not accompanied by a change in heart rate.

Second-degree and third-degree AV block represent gradations of actual block of conduction between the atrium and ventricle. The resulting symptoms are related to the slow beating rate of the ventricles.

Our assessment of PR included mean changes from baseline, the number of individual subjects with first- degree AV block or higher, and the dose-dependence of PR changes. We found dose-dependent increases in the PR interval amounting to first-degree AV block.

[Slide.]

In the 076 study, there was a dose-dependent increase in the maximum PR interval recorded at any time post-dosing including a mean change of 24 milliseconds at the 400 mg dose, and a mean change of 60 milliseconds at the 800 mg dose.

The frequency of first-degree AV block was also dose dependent. At the 400 mg dose, PR prolongation was modest with 14 percent of subjects developing first-degree AV block. At the 800 mg dose, PR prolongation was more pronounced. More than half the subjects had first-degree AV block. There were no electrocardiograms with higher than first-degree AV block, and the electrocardiographic changes were asymptomatic.

We also studied the PR interval in HIV-infected patients.

[Slide.]

In the clinical comparator studies involving nelfinavir, efavirenz, and lopinavir/ritonavir, the frequency and magnitude of PR prolongation was smaller than was observed in healthy volunteers, was not clinically significant, and was generally comparable for atazanavir and the comparators.

Approximately 3 to 10 percent of subjects receiving each treatment had first-degree AV block. No subject had higher than first-degree AV block. One subject had overdosed on over 100 tablets of atazanavir, developed first-degree AV block with a bifascicular AV block that resolved over time.

In addition to our experience in clinical trials, we also had safety experience in about 3,500 subjects in the early access program. We have recently seen junctional rhythms in two patients taking verapamil, a CYP3A4 substrate with concomitant atazanavir and other medications.

One was on an additional 3A4 inhibitor delavirdine. The patient was hospitalized with shortness of breath and atazanavir and delavirdine were discontinued. Two days later, in the continued presence of verapamil, the patient suffered a cardiac arrest, was noted to have a slower junctional rhythm at 30 to 40 beats per minute, and did not survive.

The other patient presented with syncope and a slow junctional rhythm approximately two weeks after started verapamil and atenolol for hypertension. Both of these drugs were discontinued with no interruption of atazanavir

dosing, and the arrhythmia resolved.

These two patients developed junctional rhythms likely as a consequence of CYP3A4 inhibition of verapamil metabolism.

[Slide.]

In summary, atazanavir had dose-dependent effects on the PR interval. Abnormalities in AV conduction were limited to first-degree AV block with rare exceptions. There has been no second-degree or third-degree AV block.

The incidence of PR prolongations was comparable for atazanavir and comparators in the clinical studies. Class labeling for protease inhibitors recommends caution when using concomitant medications with a narrow therapeutic index that are metabolized by CYP3A4.

Consistent with this language, caution should be taken when atazanavir is coadministered with drugs known to prolong the PR interval that are metabolized primarily by CYP3A4.

[Slide.]

Overall, to conclude, atazanavir has no effect on the QTc interval. Atazanavir has manageable effects on the PR interval that are comparable to several other HIV drugs.

As with other protease inhibitors, caution is advised when atazanavir is administered with drugs known to prolong the QTc or PR interval that are metabolized by CYP3A4.

Now, Dr. Giordano will continue with two other characteristics of atazanavir of special interest.

Characterization of Hyperbilirubinemia

DR. GIORDANO: Thank you.

In the next two presentations, I will review data that relate to two special considerations, first, bilirubin, and then, second, the unique lipid and metabolic profile that is characteristic of atazanavir.

Elevations in bilirubin were a laboratory abnormality observed early in the clinical development of atazanavir.

[Slide.]

Throughout the course of development, we learned that the elevations in bilirubin are principally unconjugated, they are predominantly mild in grade, they are reversible with drug interruption or with drug withdrawal.

We also know from clinical trials that approximately 50 percent of patients may expect to

experience a Grade 1 or a Grade 2 elevation in bilirubin and that approximately 5 percent may expect to experience Grade 4 elevation in their bilirubin. Again, these changes are reversible with drug withdrawal.

[Slide.]

In the next few minutes, we will review the physiologic mechanisms for bilirubin production and metabolism, and establish the mechanism for atazanavir-associated bilirubin elevations.

Atazanavir, like the protease inhibitor indinavir, inhibits the enzyme uridine glucuronosyltransferase, UGT, and like the benign inherited condition, Gilbert's syndrome, leads to increases in unconjugated bilirubin without hepatotoxicity.

I will then describe from a large number of treated patients from our clinical trial database the laboratory abnormalities and the clinical manifestations that relate to bilirubin. This description further dissociates bilirubin elevations from hepatotoxic processes.

Finally, we will review the plans to manage clinically relevant elevations in bilirubin should they occur in the clinic.

Increases in unconjugated bilirubin can be caused by disruption of any one of several steps in bilirubin production and bilirubin metabolism.

[Slide.]

The six principal ways in which this might occur are depicted in this schematic.

First, there can be increases in bilirubin production through red cell hemolysis or ineffective hematopoiesis.

Second, there could be impaired transport at the extracellular level as a result of alterations or interference in the binding of bilirubin to albumin.

Third and fourth, there can be disruptions of bilirubin uptake by hepatocytes or disruption within the intrahepatic transport of bilirubin.

Fifth, there can be inhibition of the intrahepatic glucuronidation step of bilirubin. This takes place prior to transport of bilirubin into the canaliculi.

Sixth, there can be disruption or impairment of bilirubin export into the bile canaliculus.

BMS is conducted in conducted in consultation with a number of experts in bilirubin

metabolism, a series of preclinical experiments and clinical assessments that have established that inhibition of UGT 1A1 is the mechanism for atazanavir's effect on bilirubin.

Hyperbilirubinemia from increased bilirubin production or other mechanisms for elevations have been excluded.

[Slide.]

In addition, the gene responsible for regulation of UGT activity is known and is the gene responsible for the Gilbert's syndrome. Genotype analysis for this gene was conducted during a large Phase II program. This assessment established that bilirubin levels in patients varied directly with their genotype. The genotype reflecting the Gilbert's syndrome resulted in the highest bilirubin levels.

The magnitude and extent of bilirubin elevations have also been extensively assessed and characterized, and allow bilirubin elevations to be further distinguished from hepatotoxic processes.

[Slide.]

This slide shows the total bilirubin and direct bilirubin levels for greater than 600 patients who have received 400 mg of atazanavir.

The increases in total bilirubin are small and consist almost entirely of unconjugated or indirect bilirubin.

As you can see, bilirubin elevations increase early, typically by the first study visit, and remain stable throughout the course of atazanavir treatment. Median total bilirubin levels remain mildly elevated to between 1.2 and 1.6 mg/dl over the course of treatment.

As you can see, there are a large number of patients out to two years in this assessment and a fair number of patients out to almost three years.

As is evident from this longitudinal graph, bilirubin levels remained stable with long-term atazanavir treatment.

As described earlier by Dr. Schnittman, ritonavir-boosted atazanavir increases both the Cmin and the AUC.

[Slide.]

Total bilirubin and direct bilirubin levels from treatment-experienced patients who receive this regimen, that is, 300 mg of atazanavir boosted by ritonavir, indicate that the median total bilirubin increases are also small. The

median total bilirubin increases ranged from 1.8 to 2.0 mg/dl.

[Slide.]

The potential clinical manifestations of elevated bilirubin has also been assessed. This assessment included the frequency of Grade 4 bilirubin elevations, the potential clinical signs, and the frequency of treatment discontinuations.

Note on this slide that in treatment-naive patients, 6 percent experienced bilirubin elevations that were greater than 5 times the upper limit of normal. Jaundice and scleral icterus occurred in approximately 11 percent of patients. The jaundice and scleral icterus was generally mild and rarely led to discontinuation of atazanavir.

In clinical trials of naive patients, fewer than 1 percent of treated patients discontinued atazanavir for hyperbilirubinemia.

Next, let's turn to ritonavir-boosted atazanavir in which the frequency of bilirubin elevations and the clinical manifestations, jaundice and icterus, were generally higher than those observed in naive patients who received unboosted atazanavir although overall, the frequency was less than anticipated.

In clinical trials to date, no subjects in the ritonavir-boosted atazanavir regimen have discontinued treatment for hyperbilirubinemia.

We also assessed concurrent Grade 3-4 elevations in transaminases and Grade 3-4 elevations in bilirubin. We found no association between hyperbilirubinemia and elevations in hepatic transaminases.

[Slide.]

This 2 by 2 table shows the frequency of Grade 3-4 elevations in ALT, and it was no different for subjects with or without Grade 3-4 elevations in bilirubin. In both instances, the frequency of ALT elevations was 4 to 5 percent. This analysis reflects a conservative assessment in which any elevation of bilirubin or ALT throughout the course of the patient's treatment was considered.

Similar assessments have been conducted in treatment-experienced patients receiving ritonavir-boosted atazanavir, and again dissociated Grade 3-4 elevations in transaminases from bilirubin elevations.

Overall, in the atazanavir development program, the frequency of transaminase elevations

were assessed and fall within the range observed with other marketed protease inhibitors.

[Slide.]

Hepatic transaminases were assessed for atazanavir in comparison to standard-of-care regimens in Phase III trials and are depicted here. In the 034 pivotal study in which atazanavir was compared to efavirenz, the rate of Grade 3-4 elevations in ALT was comparable between the regimens and ranged from 3 to 4 percent.

In treatment-experienced patients receiving ritonavir-boosted atazanavir, or atazanavir with saquinavir, the rate of transaminase elevations were again 3 to 4 percent and comparable to lopinavir/ritonavir.

In the 034 study, the 6 percent rate for atazanavir and the very low rate for lopinavir/ritonavir were outliers to the general experience.

[Slide.]

This development program included a large number of subjects co-infected with hepatitis B and C, ranging from 12 to 20 percent and generally reflective of what we are seeing in the HIV-infected population.

Subject with co-infection did not

experience bilirubin elevations more frequently than those who are not co-infected. In fact, in general, their bilirubin levels tended to be somewhat lower than those who were not co-infected.

With regard to hepatic transaminases, in general and as expected, subjects had baseline and on-study ALT levels that were more frequently elevated if they were co-infected with hepatitis B or C, however, and importantly, among co-infected subject, the frequency of transaminase elevations was similar between atazanavir and all comparator regimens.

[Slide.]

The frequency and magnitude of bilirubin elevations have been thoroughly described and the overall hepatic safety of atazanavir has been established.

The available data distinguished bilirubin elevations from hepatotoxicity based upon the biologic mechanism and based upon an absence of association between bilirubin and elevated hepatic transaminases.

Bilirubin elevations are principally cosmetic in nature and are infrequently treatment

limiting. There is no evidence for long-term sequelae. These results indicate that bilirubin elevations do not represent a significant safety concern for atazanavir.

[Slide.]

Nevertheless, BMS is committed to providing physicians and patients with a straightforward management plan which includes educational programs built upon the prior experience with the protease inhibitor indinavir.

Liver function tests monitoring beyond what is done with standard of care is not necessary.

Should elevations in bilirubin occur that are greater than 5 times the upper limit of normal, it is recommended that alternative antiretroviral therapy be considered.

Characterization of Lipid Profile

[Slide.]

I will now move to a characterization of the potential treatment benefit of atazanavir's unique lipid and metabolic profile and discuss this in context of the lipid and metabolic issues that are commonly associated with other protease inhibitors and other antiretroviral agents.

[Slide.]

The metabolic profile and problems with current protease inhibitors are familiar ones. In the next few minutes, we will demonstrate atazanavir's unique serum lipid profile both within the PI class and against other comparators.

In addition, we will observe that the favorable clinical impact of this profile is demonstrated as it reduces the need for lipid-lowering therapy when the accepted national cholesterol education program goals are applied.

The data addressing the cardiovascular risk and event rate for individuals with HIV who are receiving HAART are still evolving, nevertheless, treatment experts recommend management of hyperlipidemia and hypertriglyceridemia among patients receiving HAART that is based upon the NCEP thresholds and risk assessment.

We recognize that fat redistribution and lipodystrophy are important, but not ones that can be addressed currently by the atazanavir data. Its potential benefit will receive further attention when longer term data become available.

Current protease inhibitor treatment often

results in cholesterol, triglyceride, and other metabolic abnormalities.

[Slide.]

As seen here, a survey of the literature of the six currently prescribed protease inhibitors indicates that cholesterol is increased from baseline by roughly 30 percent and that triglycerides are increased by roughly 30 to 50 percent and sometimes higher.

These increases are large and arguably important in and of themselves, but have also been confirmed by data that indicate that up to 30 percent of U.S.-treated patients who received protease inhibitors also carry the diagnosis of hyperlipidemia.

In addition, information from managed care databases indicate that a growing number of patients who receive protease inhibitors also receive statins, by the end of 2001, 18 percent.

Atazanavir's lipid profile, as we will see shortly, differs considerably from this experience.

[Slide.]

We routinely compared a panel of cholesterol and triglyceride and other metabolic measurements, atazanavir and comparator regimens.

This included comparators of the protease inhibitors nelfinavir, lopinavir/ritonavir, and efavirenz. The presentation will focus on the longitudinal comparisons of LDL cholesterol and triglycerides.

LDL cholesterol from Study 034, depicted on this slide, patients treated with 400 mg of atazanavir in combination with zidovudine and 3TC showed no increase from baseline and LDL cholesterol.

In contrast, the comparator efavirenz, which is not as lipogenic and some protease inhibitors, resulted in an 18 percent increase in LDL cholesterol from baseline.

Similarly, when one looked at the comparative data for triglycerides, atazanavir demonstrates the same favorable profile. In Study 034, atazanavir resulted, in fact, in a 9 percent decrease from baseline in serum triglycerides. In contrast, efavirenz treatment resulted in elevations of triglycerides of 23 percent.

In addition to these data from the 034 study, there are data from two comparative Phase II studies that showed similar cholesterol and triglyceride benefits for atazanavir over the

protease inhibitor nelfinavir.

[Slide.]

Earlier, Dr. Schnittman showed the extended efficacy results for the 044 study in which atazanavir-treated subjects continued to receive atazanavir in combination with stavudine and lamivudine.

The LDL cholesterol results from this study demonstrate the same long-term benefit, that is, over two years. LDL cholesterol ranged from 103 to 108 over this two-year period of time.

[Slide.]

The nelfinavir arm was truncated at Week 60 on the previous arm because on that study, patients on nelfinavir were allowed to switch to atazanavir. The results of this switch are discussed on this slide.

As mentioned, large decreases in all cholesterol and triglyceride values were observed within four weeks and continued to 24 weeks after a switch from nelfinavir to atazanavir. The 24-week changes are depicted on this slide.

These decreases in total cholesterol, LDL cholesterol, non-HDL cholesterol, and triglycerides reflected a return to baseline levels prior to

institution or HAART therapy for this patient population.

[Slide.]

Atazanavir's potential for treatment benefit was further assessed by applying the NCEP treatment goals. NCEP provides specific management guidance for treatment of elevated cholesterol and triglycerides that is based upon cardiac risk factors and based upon the established LDL and non-HDL goals.

Most antiretroviral-treated patients fit into one of two NCEP categories either by having two or more cardiac risk factors or by having zero to 1 cardiac risk factor. Therefore, we will use the cutoffs of 130 and 160 as the relevant thresholds for assessing the need for lipid lowering intervention.

When NCEP goals are used, large differences in the need for lipid-lowering therapy are identified between atazanavir and other antiretroviral regimens.

[Slide.]

The extent to which naive patients met an NCEP treatment threshold on antiretroviral therapy are depicted for subjects treated with atazanavir

and efavirenz on this slide.

In the atazanavir arm prior to treatment, 12 percent of patients had an LDL cholesterol greater than 130, 2 percent had an LDL cholesterol greater than 160. On atazanavir treatment, there was no change in the percent of patients who met either of these NCEP goals.

In contrast, there is roughly a doubling in the percent of efavirenz-treated patients who meet or exceed and NCEP treatment goal based upon the 130 and 160 threshold goals.

[Slide.]

The data for treatment-experienced patients who underwent a single substitution of atazanavir for nelfinavir are equally compelling. At study entry and after approximately 1.5 years of nelfinavir therapy, half overall had an LDL cholesterol greater than 130. Of these, 27 percent had an LDL greater than 130, but less than 160, and 28 percent had an LDL cholesterol greater than 160.

Twenty-four weeks after a switch to atazanavir, there was a 2- to 3-fold reduction in the percentage of patients who met either of these treatment thresholds.

Similar assessment of patients meeting

NCEP thresholds have been performed for treatment-experienced patients on the 043 study in which subjects switched from failing regimens to either atazanavir or lopinavir/ritonavir.

First, look at the atazanavir-treated subjects. At baseline, 23 percent had LDL cholesterols greater than 130, 6 percent had LDL cholesterols greater than 160. After 24 weeks of treatment with atazanavir, only 7 percent had LDL cholesterols greater than 130, and none had an LDL cholesterol greater than 160.

In contrast, lopinavir/ritonavir treatment increased or did not change the percentage of patients who met the respective treatment thresholds.

[Slide.]

In summary, current clinical practice recognizes that achieving and maintaining favorable lipid and metabolic profiles for individuals who received protease inhibitors is important, but is also challenging. While hyperlipidemia may have been of secondary concern when individuals with HIV had very limited life expectancies, this is no longer true.

In the U.S. and in many other places,

long-term management of HIV is a reality and lifelong control is measured in decades, and not in months and years.

In this regard, the management of hyperlipidemia with statins and other lipid-lowering agents is problematic for patients receiving HAART. Statins further complicate already complex regimens. They introduce the possibility of added toxicity and intolerance, and they complicate already complex drug-drug interactions.

In addition, the data indicate that statins and other lipid-lowering drugs frequently to not result in achieving of the NCEP guidelines or thresholds when recipients are receiving protease inhibitors.

[Slide.]

The data are strong that atazanavir offers patients a potential treatment advantage. Lipid and triglyceride levels are not increased, cholesterol and triglyceride results are durable. This is true even when atazanavir is combined with a variety of nucleosides and with protease inhibitors despite the possibility that many of these agents may also contribute themselves to

increases in lipids.

In sum, atazanavir is a once-daily protease inhibitor with favorable lipids, offers patients unique treatment benefits. The need for lipid-lowering treatment is avoided in many atazanavir-treated naive patients. The need for lipid-lowering therapy is reduced when treatment-experienced patients are switched to atazanavir or when they institute atazanavir in lieu of other protease regimens.

Finally, treatment with atazanavir may avoid an unnecessary increase in cardiovascular risk factors.

Thank you.

Overall Risk/Benefit and Conclusions

DR. SIGAL: We can now briefly summarize atazanavir in the context of the issues that have been identified and the benefits that are established.

[Slide.]

The risks of treatment with atazanavir are well characterized. The majority of adverse events are mild to moderate and do not result in discontinuations. Hyperbilirubinemia, as you have heard, is well characterized, we believe manageable

and similar to the benign condition that is common in Gilbert's syndrome, a genetic condition with inherently reduced UGT enzyme.

Furthermore, atazanavir's mechanism for increasing bilirubin is similar to that of at least one other member of the protease inhibitor class that is in broad clinical use.

Finally, you have seen today an example of extensive characterization of cardiac electrophysiology effects of a new chemical entity, and as I mentioned at the beginning, this is becoming the evolving norm and in our studies we have established no significant effect on QT interval for atazanavir.

There is a well-characterized effect on the PR interval for which we believe there is appropriate management.

[Slide.]

Atazanavir is efficacious in the treatment of HIV infection for both treatment-naive and treatment-experienced patients. The effects, as you have seen, are durable, with controlled studies showing an efficacy past two years and patients showing benefit for three and a half years.

The lipid profile supports long-term

safety, reduces known cardiovascular risk factors, and the need for other medicines. Resistance is low in frequency and the I50L protease mutation may offer clinical utility.

Lastly and importantly, atazanavir has once daily dosing.

In conclusion, this is a novel protease inhibitor with advantages in managing the evolving viral resistance and comorbidity spectrum among HIV patients.

I would like to thank you for your attention. Steve Schnittman and Michael Giordano will now join me to answer any clarifying questions that you may have.

DR. GULICK: Thanks, Drs. Sigal, Schnittman, Lawrence, and Giordano.

We are actually going to postpone the question and answer period until after the agency presents, and then we will do a combined Q and A for both groups.

DR. SIGAL: Thank you.

DR. GULICK: Which brings us to our break. It is 10 after 10:00 and we will reconvene at 10:25. Thanks.

[Break.]

DR. GULICK: So now let's proceed with the FDA presentation. You will first hear from Dr. Kendall Marcus.

FDA Presentation

DR. MARCUS: Good morning.

[Slide.]

In today's presentation by the FDA, I will first provide you with a brief review of clinical trials submitted in support of atazanavir.

[Slide.]

Dr. Tom Hammerstrom will present his review of the efficacy data for pivotal clinical trials. Dr. Lisa Naeger will then provide a summary of the clinical virology of atazanavir. Finally, I will discuss key safety issues and provide you with a brief summary of our conclusions regarding the safety and efficacy of atazanavir.

[Slide.]

NDA 21-567 for atazanavir sulfate was submitted to the FDA on December 20th, 2002. The proposed dosage is 400 mg, once daily, to be administered as two, 200 mg capsules with food. The proposed indication is for the treatment of HIV infection.

[Slide.]

This NDA package includes two, Phase II dose-finding studies. In Study 007, atazanavir at doses of 200, 400, and 500 mg were compared to nelfinavir given at 750 mg TID. Each were given with d4T and ddi.

In Study 008, doses of 400 and 600 mg were compared to nelfinavir at a dose of 1,250 mg BID, each given with d4T and 3TC.

In these studies, patients were blinded only to the dose of atazanavir.

[Slide.]

Phase III studies included Study 034, a randomized, double-blind, placebo-controlled, multicenter study comparing atazanavir to efavirenz, each with fixed dose Combivir in treatment-naive subjects.

Study 043 is a randomized, open-label, multicenter study comparing atazanavir to Kaletra, each given with an optimized NRTI background in patients failing a PI-based regimen.

[Slide.]

Study 045 is an open-label study of highly treatment-experienced subjects who had failed at least two antiretroviral regimens containing drugs from all three classes.

In this study, a ritonavir-boosted dose of atazanavir was compared to atazanavir given in combination with saquinavir and to Kaletra. Sixteen-week data on roughly 35 patients per treatment arm were submitted with the initial NDA. Sixteen-week data for all subjects was submitted as a safety update about two months into the review.

As a result, efficacy data from this study will not be used to make a regulatory decision on this NDA.

[Slide.]

Other studies submitted with this NDA included rollover studies for subjects completing Phase II studies.

Subjects completing Study 007 were enrolled into Study 041. Subjects who had received 200, 400, or 500 mg of atazanavir were all given 400 mg of atazanavir in the rollover study, and subjects previously assigned to nelfinavir continued to receive it.

Subjects completing Study 008 were enrolled into Study 044. In this study, patients continued to receive their previously assigned dose of atazanavir, however, nelfinavir-treated subjects were switched to atazanavir 400 mg.

In addition to these studies, data was submitted from a pediatric protocol, an early access protocol, and several other smaller studies.

At this time, I would like to turn the presentation over to Dr. Tom Hammerstrom.

DR. HAMMERSTROM: The applicant has completed and submitted for FDA review two Phase III trials and two Phase II trials that are large enough to contain useful efficacy results.

One of the Phase III trials, No. 34, and both Phase II trials, 7 and 8, involve ART-naive subjects. All three trials had percent with HIV RNA levels sustained below 400 copies/ml out to 48 weeks as primary endpoint, and TAD, the time average difference from baseline, also known as BAVG or AAUCMB of log HIV RNA as secondary endpoint.

Trial 34 used efavirenz as control, Trials 7 and 8 used nelfinavir. All the arms in all three trials had two NRTIs as background regimen.

[Slide.]

One Phase III trial, No. 43, used ART-experienced patients, specifically those failing at least one prior PI regimen. This trial used Kaletra as a control with a background regimen of

two NRTIs. The primary endpoint was TAD at Week 24 and the protocol specified secondary endpoint was percent with HIV RNA sustained below 400 copies.

[Slide.]

First, I will go over the results from the three trials with ART-naive subjects.

[Slide.]

The primary findings on Trials 34, 7, and 8, on ART-native subjects, are summarized on this and succeeding slides. This slide shows the ITT results with dropouts as failures for the percent with HIV RNA sustained below 400 copies/ml.

This is abbreviated frequently as TLVR, the time to loss of viral response, and you will notice that atazanavir is equal or better than efavirenz or nelfinavir in all three trials with the percent successful for the six arms all the range 60 to 69 percent at Week 48.

At worst, the atazanavir arm was with 95 confidence no more than 1.5 percent worse than efavirenz, no more than 5 percent worse than nelfinavir in one trial, and no more than 13.8 percent worse than nelfinavir in the other trial. This trial with the lowest confidence limit is the one with the smallest sample size, therefore, the

widest confidence intervals.

[Slide.]

Now, I would like to go over in more detail, the result in the single trial with ART-experienced subjects.

[Slide.]

For Trial 43, the one reviewed trial with ART-experienced subjects, at Week 24, atazanavir was statistically significantly inferior to Kaletra with respect to both endpoints, there and there.

It was, with 95 percent confidence, 8 to 30 percent worse with respect to percent of subjects with viral load less than 400. It was, with 95 percent confidence, 0.078 to 0.4 log copies worse than Kaletra with respect to TAD.

I should remark here that the FDA analysis used the full randomized dataset of 150 patients in each arm. The applicant has presented only the first 229 subjects because that was the originally intended sample size, however, by the time the computer files were made available to the FDA, all 300 subjects had completed 24 weeks of observation, so there is no reason not to include the last 71 patients in our analysis.

I should also mention a difference in the

calculation of percent below quantitation. The subjects whose first measurement showed a rebound to above 400 copies/ml at Week 24, and had not yet reached their Week 32 visit, are counted as failures in our analysis, but they were counted as successes in the applicant's analysis.

This change of handling applies to both arms, so it will have less effect on the difference between the arms when you compare this difference to the differences between the arms in the applicant's slide.

The applicant attempted in their protocol to argue that 0.5 log copies was close enough to an active control regimen to constitute evidence of superiority to placebo. This is a problematic argument based on a generally recognized claim that the individual assay determinations at closely spaced times on the same subject have a standard deviation of about 0.5 log copies.

This is, however, a measure of assay variability and should not be equated with minimum clinically relevant difference.

[Slide.]

There are at least two recognized methods for inferring differences between test drug and

placebo in the absence of direct observation of such differences in a single randomized trial. Neither method naturally is quite as convincing as direct observation in a single trial.

Method 1 is to add together differences from two or more clinical trials, each sharing a common comparator drug. For example, add the difference between atazanavir and Kaletra from one trial to the difference between Kaletra and placebo from a second trial.

Method 2 is to collect results from a large number of representative clinical trials and to compare the observed endpoint and its confidence interval for the atazanavir plus 2 NRTI arms in Trial 43 with the same observed endpoint for the two drug and three drug arms in all the other surveyed trials.

We have already used these methods in a couple of previous NDAs, which were not presented to the committee, and we will probably expect these or other meta-analysis methods in future active control trials.

[Slide.]

This slide summarizes Method 1 for the endpoint of percent below 400 copies at Week 24.

From Trial 43, one directly observes that the atazanavir rate minus the Kaletra rate is -19 percent. That happens to be actually 46.6 percent minus 65.3 percent. The round-off is conducted after the subtraction. The standard error was 5.73 percent.

From Trial 863, in the Kaletra NDA, one directly observes that the Kaletra rate minus the nelfinavir rate was 8 percent, 79 percent minus 71 percent, with a standard error of 3.36 percent.

Finally, from Trial 511 in the nelfinavir NDA, one directly observes that the nelfinavir rate minus the placebo rate was 60 percent, 67 percent minus 7 percent, with a standard error of 5.37 percent.

Adding these three differences in the rates together, one infers that the atazanavir rate minus the placebo rate would have been -19 percent plus 8 percent, plus 60 percent, or 49 percent, with a standard error of 8.54 percent. Standard errors are not added directly, but I will skip the exact technical mathematics as to how one combines those three standard errors to get that.

As mentioned above, this is not as convincing as direct comparison. Three stages are

needed to reach placebo, each adding more uncertainty beyond that in the standard error. Trial 43, for example, used ART-experienced patients, the other two trials used patients who were either ART-naive or had limited experience.

The two drug backgrounds among the three trials, as well, differed, as well as did the baseline levels of HIV RNA and CD4 count. Nonetheless, there is a sizable imputed difference showing superiority of atazanavir over placebo, 49 percent.

[Slide.]

This slide shows a similar computation but using Trial 888, the other trial in the Kaletra NDA. This analysis has the virtue of the Trial 888, also used ART-experienced patients, so it is more directly comparable to Trial 43 than is Trial 863.

Again, the atazanavir rate minus the Kaletra rate is directly observed to be -19 percent. The directly observed difference between the Kaletra rate and the rate for an investigator-selected PI, not a placebo, was 24 percent, with a standard error of 5.69 percent.

Adding these two differences together, one

infers that the atazanavir rate minus the rate for a selected PI would be 5 percent, that is, superior imputed to atazanavir, but with a standard error of 8.07 percent.

This doesn't get one directly to the atazanavir rate minus placebo rate without reference to a large number of trials in the NDAs for all the selected PIs, so that step has been omitted in this computation.

[Slide.]

We can summarize the results from the two previous slides as follows. With respect to percent below 400 copies at Week 24, atazanavir is, with 95 percent confidence, directly observed to be between 7.9 percent and 30 percent worse than Kaletra. It can be imputed to be between 10.8 percent worse and 21 percent better than in investigator-selected PI.

Now, if one were to discount, to conduct a sensitivity analysis to reflect the added uncertainty due to pooling data across trials that are not directly comparable, one could do that by increasing the standard error by a factor of, say, 1.1, and discounting the estimated difference by a factor of 0.9.

If one does that, one gets still an imputed superiority of atazanavir over selected PI of 4.5 percent and a 95 percent interval imputed to be between 12.3 percent worse than the selected PI and 23 percent better than the selected PI.

Finally, one gets that atazanavir had an imputed 95 percent confidence interval of anywhere between 32 percent better and 66 percent better than placebo. No sensitivity analysis comparable to this slide was conducted for the placebo thing because it is clear that only a very extravagant discounting of this effect and inflation of the imputed standard error would make this lower bound equal to zero.

[Slide.]

This slide graphically presents the comparison of a number of trials in the current and previous NDAs for percent of subjects with viral load less than 400 or 500 copies while on either two-drug or three-drug regimens.

For each arm, we have plotted the observed rate and the 95 percent confidence intervals. The rates are marked on the horizontal axis, and the vertical axis just shows the different trials.

The orange interval at the top, marked

with triangles, shows the rate for atazanavir in Trial 43. Working down the graph, the light blue intervals, marked with diamonds, correspond to three drug control arms from various NDAs.

The beige intervals, marked by plus signs, correspond to two drug control arms from various NDAs. One will notice that all but one of these are lower than the atazanavir interval, and do not overlap it.

The one exception, this one, corresponded to a trial with results collected at Week 16, not Week 24, and one might reasonably conjecture that had these subjects been followed an extra eight weeks, this interval would have shifted downward.

The yellow intervals, marked by squares, down here, correspond to three drug arms with eventually approved test drugs. The atazanavir interval clearly allies with the three drug intervals and to the right in the superior direction than any of the two drug arms.

[Slide.]

The other endpoint used in this trial, and the one specified in the protocol was TAD, the time average difference from baseline in log HIV RNA. The FDA recommended against this endpoint at the

protocol stage mainly because it suffers from more missing data problems than does percent BLQ.

There is fairly convincing evidence that subjects quickly rebound to above quantitation once they discontinue ART use, so counting discontinued subjects as failures is a highly plausible solution to the missing data problem with percent BLQ.

TAD does not lend itself to such easy solutions. Two possible solutions are to replace the missing data by LOCF, the last observation carried forward. This is an idea derived from outside the HIV research area. The other method is to replace missing data by baseline, a solution which is more supported by data from trials where subjects were followed beyond drug discontinuation without starting a new therapy.

[Slide.]

This slide shows the indirect estimation of atazanavir TAD minus placebo TAD using the same three trials as with percent below 400. From Trial 43, one directly observes that the atazanavir TAD minus the Kaletra TAD was 0.26 with a standard error of 0.093.

I should also mention that in these computations, the FDA used missing data replaced by

baseline.

From Trial 863, in the Kaletra NDA, one directly observes that the Kaletra TAD minus the atazanavir TAD was 0.003 with a standard error of 0.057. From Trial 511 in the nelfinavir NDA, one directly observes that the nelfinavir TAD minus the placebo TAD was negative 0.37 with a standard error of 0.083.

I need to remind you that with this endpoint, negative numbers are good and positive numbers are bad, so the 0.26 here, that is a superiority for Kaletra over atazanavir. The 0.003 is essentially a tie. The negative 0.37 is a superiority for nelfinavir over placebo.

When one adds these three differences together, you get an observed imputed difference of negative 0.107, and that is an imputed superiority for atazanavir over placebo, but with an imputed standard error of 0.137.

[Slide.]

This slide presents a similar computation, but using Trial 888, the trial in the Kaletra NDA which used experienced patients. The computation begins as in the previous slide with atazanavir TAD minus Kaletra TAD equals 0.26. The directly

observed difference between the Kaletra TAD and the TAD for an investigator-selected PI was negative 0.104--that is a superiority for Kaletra--with a directly observed standard error of 0.078.

Adding these two differences together, one infers the atazanavir TAD minus the TAD for a selected PI to be 0.156. That is imputed superiority for the investigator-selected PI, with an imputed standard error of 0.121.

In other words, since the Kaletra TAD was 0.2X log copies better than atazanavir, but only 0.104 log copies better than the selected PI, the imputation is that atazanavir had an inferior TAD by 0.156 log copies to the selected PI.

[Slide.]

We can summarize the results from TAD as follows. Atazanavir is, with 95 percent confidence, between 0.078 and 0.44 log copies worse than Kaletra. It can be imputed to be 0.156 log copies worse than a selected PI and with approximate 95 percent confidence between 0.081 log copies better and 0.393 log copies worse than the selected PI. By the approximate in the 95 percent, I am referring to the added uncertainty due from pooling across different trials.

It can be imputed to be 0.107 log copies better than placebo, but might credibly be anywhere between 0.376 log copies better and 0.162 log copies worse than placebo.

Even without performing a sensitivity analysis to widen the confidence intervals to adjust for the extra uncertainty of incomparable trial populations, one does not conclude that TAD showed atazanavir to be superior to placebo.

[Slide.]

This slide shows the results of Method 2, comparing the 95 percent confidence intervals for TAD of log HIV RNA for a number of two-drug and three-drug arms from other NDAs. There are fewer trials than the last time we saw a slide like this because this endpoint has been used less frequently than percent below quantitation.

Again, for each arm we have the observed TAD and the 95 confidence intervals plotted on the horizontal axis, and the vertical axis just shows different trials.

Again, the orange interval at the top, marked with triangles, shows the TAD for atazanavir in Trial 43. The light blue intervals, marked with diamonds, correspond to three drug control arms

from various NDAs.

The beige intervals, marked with plus signs, correspond to two drug control arms from various NDAs. The yellow intervals, marked by squares, correspond to three drug arms with eventually approved test drugs. Remember, with this endpoint, intervals further to the left, more negative, are better. This is where you want to be down here. This is bad up here.

With respect to this endpoint, the atazanavir interval looks clearly inferior to most of the three drug intervals with two noticeable exceptions and comparable to at least half of the two drug arms.

The two exceptions, however, this one and this one, are the three drug intervals, the control and Kaletra arms from Trial 888, which is a trial with experienced patients. These two results might be taken to suggest that TAD is closer to zero for experienced subjects.

[Slide.]

In summary, atazanavir, at the indicated dose, has been compared to active controls when added to a two drug background in three trials with ART-naive subjects. With respect to percent of

subjects with HIV RNA less than 400 at Week 48, it was estimated to be equal or better than efavirenz or nelfinavir in all three trials, and with 95 percent confidence, no more than 5 percent worse than the controls in two out of three trials.

One should note that we did, but did not present, the same kind of analyses performed for Trial 43 linking nelfinavir or efavirenz to placebo for these trials, and concluded that the narrow confidence intervals or the difference between atazanavir and nelfinavir or efavirenz translate into credible imputations of superiority of atazanavir to placebo.

[Slide.]

With respect to TAD of log HIV RNA at Week 48, although we didn't present these results in detail, it was better than or equal to efavirenz or nelfinavir in two out of three trials, and in all trials, it was with 95 confidence, no more than 0.28 log copies worse than the control.

[Slide.]

In one trial out to 24 weeks with ART-experienced patients, it was statistically significantly worse than Kaletra with respect to both percent below 400 and TAD. Indirect

imputations of the difference between atazanavir and placebo gave results in which one endpoint, which the FDA regards as primary, percent below 400, appeared to demonstrate efficacy, and the second gave ambiguous results.

[Slide.]

With respect to percent below 400 at Week 24, which was the FDA recommended primary endpoint, it was indirectly inferred to be at least 33 percent better than placebo and no more than 10 to 12 percent worse than a physician-selected PI.

Compared to other arms in other NDAs receiving two or three active drug, atazanavir, in this ART-experienced trial, looked to have a better rate than any two drug arm and a rate comparable to most other three drug arms.

[Slide.]

With respect to TAD, an endpoint with undesirable missing data problems and considered secondary by the FDA reviewer, one could indirectly infer no more than that atazanavir was 0.16 log copies was, at worst, no more than 0.16 log copies worse than placebo.

Compared to other arms in other NDAs receiving two or three active drugs, atazanavir in

this ART-experienced trial looked to have a rate comparable to many other two drug arms and inferior to most three drug arms with two important exceptions, which happen to have come from ART-experienced subjects.

I will now turn the podium over to Dr. Naeger, who will give the resistance data.

DR. NAEGER: Good morning.

[Slide.]

I will be discussing the atazanavir resistance development. The focus of this discussion is that there are different resistant pathways for atazanavir. Atazanavir has a unique pathway in treatment-naive patients with development of a key mutation, however, in treatment-experienced patients, atazanavir follows a common protease inhibitor resistance pathway with the development of mutations seen with other protease inhibitors.

[Slide.]

To assess the potential for atazanavir resistance development and to identify amino acids associated with atazanavir resistance, the applicant utilized in vitro selection.

Three HIV strains were passaged at

increasing concentrations of atazanavir, and resistant viruses were selected at four to five months. These resistant viruses exhibited 93- to 183-fold changes in atazanavir resistance, which is a change in the IC50 compared to reference strain.

The key amino acid changes are highlighted for each of the three resistant viruses - a methionine at position 46, which changed to isoleucine or M46I. In addition, there was an A71V, I84V, N88S, and in another strain there was a unique mutation I50L, which is different from the amprenavir-associated mutation I50V.

This demonstrates that there are different possible pathways for atazanavir resistance. One pathway contains and I84V mutation, which is associated with resistance to other protease inhibitors, and another pathway contains the unique mutation I50L.

[Slide.]

The applicant has provided evidence that atazanavir resistance corresponds to the I50L and A71V mutations by constructing recombinant viruses from eight clinical isolates. These viruses show 2- to 17-fold changes in IC50 for atazanavir compared to a reference strain.

[Slide.]

Importantly, recombinant viruses containing the I50L mutation either with or without the A71V mutation remains susceptible to other protease inhibitors. This suggests that treatment-naive patients that develop the I50L mutation in their virus would still have other treatment options.

Another interesting finding is that the I50L mutation results in replication-impaired viruses. The addition of the A71V mutation restores some viability to the virus and suggests that this is a compensatory mutation.

[Slide.]

Now, turning to atazanavir clinical resistance, I will present the analyses in three parts starting with the mutations associated with atazanavir resistance from both treatment-naive studies 007, 008, and 034, and also treatment-experienced trial 009 and 043. Our analyses does not include Study 045.

This is using evaluable clinical isolates from patients who were on atazanavir treatment and experienced virologic failure.

Next, will be a baseline phenotypic and

genotypic analyses, and then finally, an examination of cross-resistance with atazanavir and other protease inhibitors.

[Slide.]

There were 160 evaluable isolates from patients on atazanavir regimens who experienced virologic failure. Fifty isolates, or 31 percent, were atazanavir resistant, which is defined as greater than 2.5-fold change in the IC50 for atazanavir comparator reference.

I would like to point out that four of these 50 isolates were from the rollover study 041 and 044, and developed the I50L mutation on atazanavir treatment.

There were 93 evaluable isolates from the naive trials, 15 percent, or 14 isolates, were atazanavir resistant with a median fold change of 8.7. The percentage of atazanavir resistance goes up in treatment-experienced trials, whereas, 63 evaluable isolates from Trial 009 and 043, 51 percent were atazanavir resistant with a median 11-fold change in atazanavir resistance.

[Slide.]

As I said, there were 14 atazanavir-resistant clinical isolates from the treatment-naive studies. Eleven

of these developed the I50L mutation, so almost 80 percent. They had a median 9-fold change in atazanavir resistance, and 7 of the 11 also developed the A71V mutation.

The development of the I50L mutation ranged from 2 to 80 weeks, averaging 40 weeks.

[Slide.]

An examination of the clinical isolates that developed the I50L mutation shows an almost 11-fold change from baseline for atazanavir. The fold change from baseline for other protease inhibitors is less than 1, indicating increased susceptibility to other protease inhibitors. This suggests that the I50L mutation will remain susceptible to other protease inhibitors.

[Slide.]

There were 32 isolates that were atazanavir resistant and virologic failures from the treatment-experienced trials; 21 were on the 400 mg atazanavir treatment. The mutations that developed included an A71V or T, an I84V, and an N88S or D. As you recall, all these mutations were selected in the in vitro selection experiments.

[Slide.]

There were 11 clinical isolates on

concomitant atazanavir/saquinavir treatment. Again, the mutations that developed include I84V, A71V or T, L90M, and M46I. These mutations were often seen in combination.

It is not surprising that no I50L developed because of the concomitant saquinavir selection pressure here.

[Slide.]

These 32 atazanavir-resistant isolates that were virologic failures show a median 11-fold change in atazanavir susceptibility. The cross-resistance of these isolates show that 37 percent and 47 percent were also resistant to amprenavir and lopinavir respectively with median fold changes in atazanavir susceptibility of 1.7 and 2.0, however, over 80 percent of these isolates were resistant to saquinavir, ritonavir, indinavir, and 100 percent were resistant to nelfinavir with median fold changes in atazanavir susceptibility ranging from 5 to 28. So, these atazanavir-resistant isolates are cross-resistant.

[Slide.]

Now turning to baseline analysis.

[Slide.]

The baseline phenotypic analysis of the

treatment-experienced trial 009 and 043 show that 56 percent of the isolates were resistant to at least protease inhibitor at baseline; 74 percent were resistant to at least one NRTI at baseline, and 20 percent resistant to at least one NRTI at baseline, so it is a fairly treatment-experienced patient population entering these two trials.

[Slide.]

Twenty-four percent of the isolates from these two trials showed atazanavir resistance at baseline.

[Slide.]

Examining the cross-resistance to other protease inhibitors at baseline, if the isolates were resistant to atazanavir at baseline, 100 percent were also resistant to nelfinavir. About 50 percent were resistant to indinavir and lopinavir, and greater than 50 percent were resistant to ritonavir and saquinavir.

[Slide.]

Now, looking at the response based on baseline genotype or the mutations that were present at baseline showed that if the isolates had an I84V mutation at baseline, over 90 percent failed if they were on atazanavir treatment

compared to other comparative treatment.

If they had an L90M at baseline, 74 percent failed compared to 43 percent. With an A71V mutation at baseline, 62 percent failed on atazanavir treatment compared to 33 percent. With a change at N88, 56 percent failed on atazanavir compared to 18 percent on other treatments, and with an M46I at baseline, 68 percent failed compared to 46 percent.

This suggests that if the virus has any of the mutations at baseline, response to atazanavir treatment might not be as effective as other treatments.

[Slide.]

Turning to cross-resistance.

[Slide.]

First, cross-resistance by phenotype. Of the atazanavir-resistant isolates--again, this is using baseline phenotypic data from all studies--of the atazanavir-resistant isolates, 100 percent were resistant to nelfinavir, and there is a high cross-resistance to other protease inhibitors, with amprenavir having the lowest percent of 51 percent.

Isolates that were resistant to other protease inhibitors showed a high cross-resistance

with atazanavir with 61 percent to 95 percent of the isolates resistant to atazanavir.

[Slide.]

Cross-resistance by genotype. In isolates that contained an I84V or G48V, greater than 90 percent were resistant to atazanavir. Around 60 percent of the isolates that contained an L90M or V82 were resistant to atazanavir, and 38 percent with the D30N were resistant to atazanavir. Only 12 percent with the I50V were resistant to atazanavir.

So, although the I50V confers resistance to amprenavir, you see here 100 percent, it generally does not confer resistance to atazanavir.

Again, the I50L mutation confers resistance to atazanavir, but remains susceptible to all other PIs.

[Slide.]

Another way to look at cross-resistance is by the number of protease inhibitors that isolates are resistant to. Of the isolates that were resistant to one or two PIs, less than 20 percent were resistant to atazanavir, however, atazanavir loses effectiveness as isolates become resistant to three or more PIs, with greater than 80 percent of the isolates that are resistant to four or five

other PIs are also resistant to atazanavir.

[Slide.]

This is shown in this slide also that the median fold change in atazanavir susceptibility increases as the number of PIs that isolates are resistant to goes up. This also gives you some idea of what a possible breakpoint for atazanavir might be somewhere between 2- to 6-fold.

[Slide.]

In summary, there are different resistant pathways for atazanavir. One pathway that appears to develop primarily in treatment-naive patients includes a unique mutation at I50L. The I50L mutation is specific for atazanavir resistance and is the predominant mutation developing in antiretroviral therapy-naive patients.

In the studies that we analyzed, 80 percent of the atazanavir-resistant isolates developed the I50L.

Importantly, viruses that develop the I50L mutation remain susceptible to other protease inhibitors. The other pathway occurring in treatment-experienced patients develops mutations associated with resistance to other protease inhibitors and confers cross-resistance.

These mutations, such as L90M, I84V, a change at N88 or A71V or T, appear to confer atazanavir resistance and reduce the clinical response to atazanavir.

So, the evidence suggests that if other PI mutations are present at baseline, atazanavir resistance develops through the latter pathway rather than the I50L pathway.

Finally, if isolates are resistant to three or more protease inhibitors, they are more likely to be resistant to atazanavir.

Now, I will turn it back over to Dr. Marcus.

DR. MARCUS: Hyperbilirubinemia was the most common drug-related lab abnormality experienced by atazanavir-treated subjects. As discussed by the applicant, this appears to be due to inhibition of UDP- glucuronosyltransferase 1A1 or UGT1A1 by atazanavir.

[Slide.]

Grade 1-2 elevations in clinical trials were defined at 1.1 to 2.5 times the upper limit of normal. A Grade 3 elevation of total bilirubin was defined as greater than 2.5 times the upper limit of normal, and Grade 4 elevations were defined as

greater than 5 times the upper limit of normal.

The upper limit of normal for total bilirubin varies slightly from lab to lab, but is generally defined as less than 1 to 1.5 mg/dl, and the upper limit of normal of direct bilirubin is generally defined as less than 0.2 to 0.5 mg/dl.

[Slide.]

The hyperbilirubinemia that was observed in dose-finding Phase II clinical trials was clearly dose dependent as can be seen in this chart. The incidence of Grade 3-4 elevations in total bilirubin ranged from 20 percent for subjects receiving the 200 mg dose of atazanavir to 50 percent for patients receiving 600 mg.

A management strategy of dose reduction for severe hyperbilirubinemia was utilized in clinical trials of atazanavir. Patients with confirmed Grade 4 elevations of total bilirubin underwent dose reduction. Subjects receiving the 400 mg dose of atazanavir were dose reduced to 200 mg. If Grade 4 hyperbilirubinemia persisted or recurred, these patients were discontinued from treatment.

Insufficient data regarding the efficacy of a reduced dose of atazanavir was provided with

this NDA and as a result, will not be recommended for general clinical practice.

[Slide.]

The incidence of any grade elevation of total bilirubin was common in clinical trials and ranged from 74 percent in treatment-experienced study 043 to over 90 percent in dose-finding studies 007 and 008.

Grade 3-4 elevations ranged from 20 to 40 percent across these studies. The mean total bilirubin was 1.7 mg/dl for treatment-naive subjects in Study 034, 1.4 mg/dl for treatment-experienced subjects in 043, and 1.3 mg/dl in highly treatment-experienced subjects receiving atazanavir 400 mg in combination with saquinavir in Study 045.

[Slide.]

Jaundice and/or scleral icterus was reported in 15 to 21 percent of patients receiving the 400 mg dose of atazanavir. Despite this, treatment discontinuation due to either event was uncommon. This may have been due in part to dose reduction as the management strategy for Grade 4 hyperbilirubinemia, which I will discuss further in a moment. It may be postulated that treatment

discontinuation for these adverse events may be more common in clinical practice.

[Slide.]

Five percent of subjects in Study 034 underwent dose reduction for confirmed Grade 4 hyperbilirubinemia and 1 percent of subjects in Study 043. This led to the need for treatment discontinuation for Grade 4 hyperbilirubinemia for only one subject in Study 034.

The applicant is currently proposing that patients discontinue treatment with atazanavir for confirmed elevations of bilirubin greater than 5 times the upper limit of normal. As a result, one can reasonably expect that about 5 percent of treatment-naive subjects and about 1 percent of treatment-experienced subjects will discontinue treatment for hyperbilirubinemia.

[Slide.]

This graph might be a little confusing. It shows mean total and direct bilirubin as grouped by category of total bilirubin - the categories being less than 2.5 mg/dl, 2.5 to 5.0 mg/dl, and greater than 5.0 mg/dl.

I have taken all of the bilirubins reported in Study 034 and grouped them by these

categories and calculated the means. The mean direct bilirubin reported with each category of total bilirubin then represents the mean direct bilirubins that corresponded to the total bilirubin values.

The mean direct bilirubin was minimally elevated across all categories of total bilirubin, supporting inhibition of UGT 1A1 as the mechanism of hyperbilirubinemia.

[Slide.]

Severe elevations of total bilirubin, which I have defined here as greater that 10 mg/dl, were uncommon and occurred in only 10 patients across clinical trials. The highest total bilirubin reported in clinical trials was 12.1 mg/dl. In these patients, elevations of direct bilirubin and other LFTs were more common.

Four out of the five patients who had other indices of hepatic injury or inflammation were co-infected with the hepatitis virus, and the remaining subject appeared to have a resolving hepatitis at the time of study enrollment.

[Slide.]

In Study 007, all grades of LFT abnormalities were more common in atazanavir-treated

subjects as compared to nelfinavir. In this study, Grade 3-4 LFT abnormalities were more common in atazanavir-treated subjects than in nelfinavir-treated subjects.

In Study 008, all grades of LFT abnormalities were also more common in atazanavir-treated subjects, however, Grade 3-4 LFT abnormalities were slightly more common in nelfinavir-treated subjects.

Discontinuations for LFT abnormalities were similar between atazanavir and nelfinavir-treated subjects when treatment arms for these two studies were combined.

[Slide.]

In Study 034, all grades of LFT abnormalities with the exception of total bilirubin were slightly more common in efavirenz subjects as compared to atazanavir. However, the incidence of Grade 4 abnormalities was similar.

[Slide.]

Discontinuations for abnormal elevations of LFTs excluding isolated hyperbilirubinemia appeared to occur with similar frequency in atazanavir-treated subjects relative to comparators. The majority of these subjects were

co-infected with hepatitis B or C.

Three subjects receiving atazanavir and one subject receiving ritonavir/saquinavir had no apparent risk factors for hepatic inflammation or injury.

[Slide.]

In summary, inhibition of UGT 1A1 by atazanavir appears to result in a predominantly unconjugated hyperbilirubinemia that is reversible upon discontinuation of treatment. The risk of hepatic toxicity seen with atazanavir use appears to fall within the range of that seen with other currently marketed antiretroviral agents.

[Slide.]

It was first observed in Phase II dose-finding studies that use of atazanavir resulted in minimal changes in lipid profiles as compared to nelfinavir. Use of nelfinavir was associated with significant increases in total and LDL cholesterol and fasting triglycerides.

These dose-finding studies were not specifically designed to collect this data, so fasting lipid profiles were available for only one-half to three-fourths of patients. However, these findings were confirmed in Phase III studies.

[Slide.]

At Week 48, in Study 034, minimal changes in fasting total and LDL cholesterol were observed in atazanavir-treated patients while significant increases in these parameters were seen in efavirenz-treated patients.

Atazanavir use was associated with a modest decrease in fasting triglycerides while efavirenz use was associated with a significant increase. HDL levels increased significantly in both treatment arms, however, the increase in HDL was greater in efavirenz-treated subjects.

[Slide.]

Categorical analysis of lipid profiles revealed that more patients receiving efavirenz as compared to atazanavir experienced significant elevations in total and LDL cholesterol and fasting triglycerides that might require dietary modification or medical management.

[Slide.]

At Week 24, in Study 043, atazanavir-treated subjects experienced minimal decreases in fasting total and LDL cholesterol and in fasting triglycerides while Kaletra-treated subjects experienced elevations in all of these lipid

parameters.

Differences in lipid profiles between treatment arms were statistically significant. Patients in both treatment arms experienced increases in fasting HDL.

[Slide.]

More patients in this treatment-experienced study had elevated lipids at baseline as compared to those in treatment-naive study 034. In this study, 5 to 12 percent of patients had significant elevations of total or LDL cholesterol or fasting triglycerides at baseline as compared to 2 to 4 percent of patients in Study 034.

At Week 24 of treatment, fewer atazanavir-treated subjects had elevated total or LDL cholesterol than at baseline while increases were observed in Kaletra-treated patients. No significant change was seen in the percentage of atazanavir-treated subjects with elevated triglycerides.

[Slide.]

This slide shows the mean change in fasting triglycerides over time in the dose-finding studies 007 and 008. The yellow lines represent atazanavir-treated subjects and the white lines

represent nelfinavir-treated subjects.

Nelfinavir-treated subjects experienced a rapid increase in fasting triglycerides that was sustained throughout treatment. Atazanavir-treated subjects initially appeared to have modest decreases in fasting triglycerides, however, the levels appeared to increase slightly over time. This may suggest that other factors may also contribute to changes in fasting triglycerides.

[Slide.]

Use of atazanavir did not appear to result in a lower incidence of patient- and investigator-reported lipodystrophy events through one to two years of treatment.

[Slide.]

Significant cardiovascular events were rare in atazanavir clinical trials and the duration of follow-up too short to reach any conclusions regarding the reduction of cardiovascular risk with the use of atazanavir as compared to other protease inhibitors or to efavirenz.

[Slide.]

In conclusion, the favorable lipid profiles associated with atazanavir use appeared to persist through two years of treatment although

data from Phase II trials is limited by study design.

Benefits for treatment-experienced patients are less well defined as factors other than current protease inhibitor use appear to contribute at least to hypertriglyceridemia. Lipid effects do not appear to be associated with a reduced incidence of lipodystrophy through two years of treatment, and cardiovascular benefit at this time remains unclear.

[Slide.]

Preclinical evaluation of atazanavir for potential effects on cardiac conductivity were remarkable for modest inhibition of HERG channels at high concentrations. In Purkinje fiber studies, it was also noted to produce a dose-dependent increase in the mean action potential duration.

As a result of these findings, studies were undertaken by the applicant to examine potential effects of atazanavir on the QT interval.

[Slide.]

As mentioned previously by the applicant, Study 076 was a three-treatment, three-period crossover study where subjects were assigned to receive placebo 400 mg or 800 mg of atazanavir in

six different sequences. Each treatment period was separated by a washout period of at least 14 days. Twelve EKGs were obtained over a 24-hour period at baseline and on Day 6 of each treatment period.

[Slide.]

In this study, unlike previous studies designed to evaluate EKG changes with atazanavir use, a dose-dependent increase in the heart rate was noted. This effect was detected in this study possibly due to larger number of enrolled subjects as compared to previous studies and due to the 14-day washout period between treatment arms.

[Slide.]

I have two graphs here plotting heart rate against corrected QT intervals obtained from Study 076 in the placebo treatment arm. The graph on the left shows the QT intervals calculated by Bazett's correction and the graph on the right shows QT intervals calculated using Fridericia's correction.

As you can see from these graphs, Bazett's correction appears to overcorrect the QT interval as the heart rate increases. Fridericia's correction formula appears to provide a more consistent correction over a range of heart rates.

The placebo-corrected mean change in the

QT interval, as measured as Tmax, from baseline to the 800 mg dose is 7.9 milliseconds when calculated using Bazett's correction.

The mean change when calculated using Fridericia's formula is -1.6 milliseconds. The 95 percent confidence interval for the mean change using Fridericia's correction include zero.

[Slide.]

In Studies 034 and 043, no significant differences in the incidence of prolonged QT intervals was observed between atazanavir and comparators.

[Slide.]

All events, cardiovascular events potentially related to arrhythmia were reviewed. No events related to atazanavir use and prolongation of the QT interval were identified.

[Slide.]

Although data from placebo-controlled study 076 is limited by the lack of a positive control, this study may indicate that atazanavir has little or no effect on the QT interval, however, the overall risk is unknown.

No signal for any significant risk or an increased risk relative to comparators was

identified in clinical trials.

[Slide.]

My next topic will be the effects of atazanavir on the PR interval.

[Slide.]

Multiple mechanisms can lead to prolongation of the PR interval and varying degrees of AV block. Medications can cause PR interval prolongation through direct effects on the AV node, through calcium channel blockade or through other mechanisms.

Medical conditions, such as fibrosis of the conduction system, ischemic heart disease cardiomyopathy, and myocarditis can also cause PR interval prolongation and AV block.

In pharmacokinetic studies undertaken to evaluate effects on the QT interval, atazanavir caused a dose-dependent prolongation of the PR interval. In vitro studies also indicated that it was a moderate calcium channel inhibitor, and this is the likely mechanism for PR interval prolongation.

[Slide.]

The most common abnormality observed in EKG in clinical trials was first-degree AV block.

While first-degree AV block appears to be largely asymptomatic, there may be clinical scenarios where significant prolongation of the PR interval may impact upon patient stability.

According to the ACC 2002 guidelines on pacemaker placement, PR intervals greater than 300 milliseconds may lead to worsening to symptoms of CHF in patients with LV dysfunction. Expert consensus is the primary basis for recommendation for pacemaker placement in these patients.

[Slide.]

This graph shows the mean PR intervals of subjects taking the placebo 400 mg and 800 mg doses of atazanavir in Study 076. As mentioned previously, 60 percent of patients receiving the 800 mg dose of atazanavir were observed to have first-degree AV block.

The highest PR interval recorded in this study was 324 milliseconds in a patient receiving the 300 mg dose.

[Slide.]

In clinical trials, EKGs were collected at three time points - at baseline or trough prior to dosing, at two to three hours after dosing, and at six to 12 hours after dosing.

The mean PR intervals that I am presenting here were recorded at the time corresponding to maximum atazanavir concentration, two to three hours post-dose. Although the mean intervals seen at this time point were not significantly different than those seen at other time points.

[Slide.]

In Study 034, the mean PR interval for efavirenz at two to three hours post-dose was 153 milliseconds. The mean PR interval for atazanavir was 7 milliseconds longer. Maximum recorded PR intervals for atazanavir-treated patients in this trial ranged from 265 to 307 milliseconds.

[Slide.]

First-degree AV block was slightly more common in atazanavir-treated subjects as compared to the efavirenz-treated subjects in Study 034.

[Slide.]

The mean PR interval for atazanavir-treated subjects was 6 milliseconds longer than the mean PR interval for nelfinavir-treated subjects in rollover study 041, however, this difference was not statistically significant.

[Slide.]

The incidence of first-degree AV block in

nelfinavir-treated patients appeared to be similar to that seen in atazanavir subjects participating in the rollover studies.

[Slide.]

Finally, the mean PR intervals of atazanavir and Kaletra-treated subjects were similar at all time points.

[Slide.]

The incidence of first-degree AV block also appeared to be similar between atazanavir and Kaletra-treated patients.

[Slide.]

I would like to just briefly mention two cases where use of atazanavir may have been associated with more serious conduction abnormalities.

In this case, a 43-year-old male ingested a large number of atazanavir, 3TC, and d4T pills in an apparent suicide attempt. The patient was noted to have a severely prolonged PR interval with bifascicular block. These abnormalities resolved five days after drugs were withheld.

[Slide.]

In this case, a 50-year-old male was hospitalized on Day 11 of treatment with

atazanavir, delavirdine, 3TC, and tenofovir for angina and shortness of breath. He was also receiving verapamil for hypertension.

EKG on admission was remarkable for a junctional rhythm. Antiretroviral medications were held, however, the patient continued to receive verapamil. One day following admission, an EKG showed persistence of the junctional rhythm, and the next day the patient was found unresponsive with an idioventricular rhythm.

[Slide.]

In conclusion, atazanavir appears to cause a dose-dependent prolongation of the PR interval. The incidence of first-degree block seen in atazanavir-treated patients appears to be similar in incidence observed in patients treated with comparators.

Severe PR prolongation or more serious events appear to be rare.

[Slide.]

I just wanted to briefly mention the pediatric ACTG protocol that continues to enroll patients in order to evaluate safety and pharmacokinetics of atazanavir in infants greater than 3 months of age, children, and adolescents.

Adverse events in children appear to be generally similar to those seen in adults with hyperbilirubinemia being the most common adverse event reported. Unfortunately, due to wide variability of PK data, a dose has not yet been defined for any of the age groups.

[Slide.]

I also just wanted to briefly highlight drug-drug interactions.

[Slide.]

Drugs that fall into the following categories can potentially have significant interactions with atazanavir. Those that are CYP3A inhibitors, inducers, or substrates, drugs that increase pH, drugs that cause PR prolongation, and 2C9 or 1A2 substrates.

[Slide.]

Diltiazem is a CYP3A4 substrate and also prolongs the PR interval. Atazanavir, when coadministered with diltiazem, raised the Cmax and area under the curve of diltiazem by 100 percent. More subjects experienced first-degree AV block when receiving the combination of atazanavir and diltiazem than when either drug was administered alone.

The longest PR interval observed in this study was 302 milliseconds in one subject receiving the combination of atazanavir and diltiazem.

[Slide.]

Ethinyl estradiol and norethindrone are both CYP3A4 substrates, and ethinyl estradiol is also a UGT 1A1 substrate. Because of this, concomitant use of oral contraceptives and atazanavir was examined for potential drug interactions.

When coadministered with Ortho-Novum 7/7/7, atazanavir increased the Cmax and area under the curve of both ethinyl estradiol and norethindrone. This should not have an impact on the efficacy, but may impact safety.

As a result of these findings, it may be recommended that physicians prescribing oral contraceptives should attempt to use the lowest effective dose.

[Slide.]

In conclusion, atazanavir appears to have antiviral activity similar to efavirenz or nelfinavir in treatment-naive patients. It was inferior to Kaletra in treatment-experienced patients.

Potential treatment advantages include a low pill burden and a unique resistance profile in treatment-naive subjects.

[Slide.]

The hyperbilirubinemia associated with the use of atazanavir appears to be due to inhibition of UGT 1A1 and is reversible with treatment discontinuation.

The risk for hepatotoxicity appears to fall within the range of that seen with other antiretroviral medications.

[Slide.]

Atazanavir causes a dose-dependent prolongation of the PR interval. Clinically significant events due to this effect appear to be rare. Effects of atazanavir on the QT interval appear to be minimal.

[Slide.]

One other potential treatment advantage for atazanavir appears to be its lack of effect on lipid profiles. Despite this, patient and investigator reported lipodystrophy events appeared similar between atazanavir and comparators at least through two years of treatment.

Finally, the impact on cardiovascular

events is unknown at this time.

DR. GULICK: Thanks, Drs. Marcus, Naeger, and Hammerstrom.

We are now ready go into the question and answer period for both the sponsor and the agency. Just to remind the committee we have plenty of time for discussion in the afternoon, so let's try to stick to questions of clarification or information at this time.

Dr. Morganroth would like to start us off.

Questions from the Committee

DR. MORGANROTH: I have a question for the sponsor. On the 076 study, can you tell us what percentage of the subjects were female and what the results of the central tendency and outlier analysis was in the females compared to men? Then, I have a follow-up question after that.

DR. LAWRENCE: In the 076 study, approximately 25 percent of the subjects were females. At the 400 mg dose in that study, as well as in our clinical program, there was no gender difference with respect to PR change or QT change.

DR. MORGANROTH: If you interpret that study as using Fridericia's as a negative trial and you saw no events in QT analysis in the Phase

II/III program and no signals, and you weren't even able to reach an IC50 in HERG preclinically, why is it that you are recommending that prescribers not use concomitant QT-prolonging drugs with your drug?

DR. LAWRENCE: Our specific recommendation is caution when the concomitant drug that prolongs QT interval is metabolized by 3A4, so we are advising caution in the setting of a potential PK interaction, but our drug intrinsically doesn't appear to affect QT.

DR. MORGANROTH: Thank you.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: Also on the 076, you found the dose effect on the PR interval of atazanavir, doses of 400 and 800. My question is what about the boosted 300, 100, atazanavir/ritonavir, and that it would produce exposures above what 800 mg of atazanavir would?

DR. SCHNITTMAN: In fact, we have looked at exposures of 300 and 100, and they are less than what is seen for 800 mg. The primary effect of the ritonavir is to delay the elimination. There is actually a very small increase in Cmax of about 20 percent relative to a 400 mg dose by itself.

DR. FLETCHER: But what about at Cmin?

DR. SCHNITTMAN: The Cmin of the 800 is higher, but still higher than even the 5- to 8-fold increase that we see with the 800 mg, as well.

DR. GULICK: Dr. Kumar and then Dr. Wood.

DR. KUMAR: Can you comment on what happened to the lipid profile when the drug was combined with ritonavir in 045, similar to the slide you have, your slide 90?

DR. GIORDANO: We did look at the lipid values, LDL cholesterol and triglycerides on the 045 study, and similar to what we have described in other studies, there were significant differences between lopinavir/ritonavir and atazanavir/ritonavir with regard to LDL cholesterol and triglycerides.

DR. GULICK: You wanted to see the data?

DR. GIORDANO: Did you want to see the data?

DR. KUMAR: Yes, that would be great.

DR. GIORDANO: I would be happy to pull up the slide of the 045 study.

[Slide.]

DR. GIORDANO: These are the LDL cholesterols over time, 16 weeks. In green and in blue are the two atazanavir treatments, one with

ritonavir in green, in orange is the lopinavir/ritonavir. Remember that this reflects a direct switch from previous therapy to the new therapy without a washout period.

We have a similar slide for triglycerides.

[Slide.]

DR. GIORDANO: 6J8. Again, we see that there is somewhat of a decrease in triglycerides over 16 weeks, and a further increase in triglycerides on the lopinavir/ritonavir treatment.

DR. GULICK: Dr. Wood.

DR. WOOD: My question again relates to the QT and the PR intervals. My understanding is from the 076 studies, that the EKGs were done over a 24-hour period. Do you all have any data regarding QT and PR intervals after individuals have been dosed chronically with atazanavir after weeks or months of exposure?

DR. SCHNITTMAN: The chronic data comes from the clinical trials. In 043, 034, 045, we had multiple ECGs, number one, that were done on a given day, three that were done on a given day, and then done at least four to eight times more, three times, as well, that confirm those responses.

DR. WOOD: A second related to the PR

interval is that first-degree AV block is very common in clinical practice, and did you all do any substudy analysis of individuals who may have had pre-existing first-degree AV block in terms of PR prolongation and whether or not there was a greater percentage of prolongation in those individuals?

DR. LAWRENCE: We couldn't look precisely to answer that question, in part because for the latter studies, protease inhibitor therapy wasn't interrupted before study drug was initiated, so the baseline is a little bit complicated, but where we could look at it, it seems that about 2 percent of subjects came in with a PR that was modestly prolonged, and it was infrequent that it got significantly further prolonged on study drug.

DR. GULICK: Dr. Tephly and then Dr. Fish.

DR. TEPHLY: Yes, I have about four or five questions.

The first one, what is the distribution of this drug?

DR. SCHNITTMAN: It is distributed widely and to give a further description of that, I want to turn to our PK person. While he is walking up here, there is penetration into the CNS, but it is of a low order similar to other protease

inhibitors.

DR. TEPHLY: That was my next question actually.

DR. SCHNITTMAN: And it penetrates also into the semen.

DR. TEPHLY: While he is walking up, you might answer this one then. Is morphine used to any extent in AIDS patients?

DR. SCHNITTMAN: Excuse me?

DR. TEPHLY: Is morphine used in AIDS patients?

DR. SCHNITTMAN: In terminal cases.

DR. TEPHLY: I think the answer is yes.

DR. SCHNITTMAN: Yes.

DR. TEPHLY: The question I have is do you realize that morphine also is a CYP3A4 substrate, and I didn't see any opioids tested in terms of drug-drug interactions. Is that true?

DR. SCHNITTMAN: To date, yes. A methadone study is currently ongoing now, because we realized it is an important drug interaction consideration. That is currently ongoing.

Dennis, do you want to address the other question?

DR. GULICK: Can you introduce yourself,

as well.

DR. GRASELA: Dennis Grasela, Bristol-Myers Squibb.

I don't really have anything further to add to what Dr. Schnittman has said. The drug is distributed in the body and does hit some of the reservoir sites.

DR. TEPHLY: Well, what is the mechanism of lipid lowering for this chemical?

DR. GIORDANO: We have looked at a number of preclinical experiments trying to ascertain and elucidate the mechanism by which atazanavir has a different effect on lipids from other protease inhibitors.

Compared to other protease inhibitors, atazanavir is less likely to induce lipogenesis in adipocytes and in hepatocytes. It also has differential effects on glut [?] 4, but those are relative to other protease inhibitors.

DR. TEPHLY: But there is no effect on the reductase, HMG CoA reductase?

DR. GIORDANO: I am not sure of the answer to that question. Does it have no effect on HMG CoA reductase, is that the question?

DR. TEPHLY: Yes.

DR. GIORDANO: Dr. Parker, who is in our group, conducted most of the preclinical work, will be able to help us out on that.

DR. GULICK: Please introduce yourself.

DR. PARKER: Rex Parker from Bristol-Myers Squibb Preclinical.

While we haven't specifically addressed HMG CoA-reductase, we have done a number of studies that have surveyed potential areas of interaction of atazanavir in comparative studies with other PIs.

You see on the slide, areas for molecular and cellular interactions with transport hepatocyte lipogenesis at the site differentiation, and importantly, gene expression profiles in both adipocytes and hepatocyte models, and all of these studies converge on the finding that we reproduce what other labs have shown with several other PIs as comparators, but that atazanavir is relatively devoid of activities on each of these pathways or molecular points of intervention, and specifically does not have any effect on cholesterol synthesis rate, on triglyceride synthesis rate, which would address your question about the reductase.

DR. TEPHLY: So, there would be no effect

on the jerenial [?] system?

DR. PARKER: No effect as we know it with current studies.

DR. TEPHLY: Is there any effect on absorption from the gut, other substances such as vitamin B?

DR. GRASELA: At this point, we have no data to address that question.

DR. TEPHLY: I see that that kind of information was sort of missing from the compilation of information we got, but it is of some concern if there is an effect on lipid transport across the GI tract, either direction.

It would be interesting, and I doubt that there would be a problem, but it is something that might be addressed.

I do have a couple more questions, and that is, the patients who showed hyperbilirubinemia, were they tested for Gilbert's before the study began? I may have missed that.

DR. GIORDANO: Routine genotyping for Gilbert's was not conducted on all patients on all studies. We do have data from select Phase II studies to look at Gilbert's genotype with regard to the 7/7 genotype.

DR. TEPHLY: Because it is fairly common. It is 40 percent of the population, and I noticed that 40 percent of your 400 mg dose, at least at first, I think was affected. So, I was just wondering whether you just perturbed patients who had Gilbert's to begin with.

DR. GIORDANO: Undoubtedly. We know that we included patients with the Gilbert's syndrome in our clinical program. The number that we came up with, with regard to the frequency, was closer to 10 percent of our patients on clinical study, which appears to be reflective of the general number in the population, so they were not excluded.

DR. TEPHLY: Is that 10 percent homozygotes?

DR. GIORDANO: Yes, 10 percent 7/7s.

DR. TEPHLY: You didn't look at any other?

DR. GIORDANO: We also looked at 6/7s, 7/8s, 6/6s on our Phase II program. We conducted a cross-sectional study through one, Phase II study. Most of those samples came from the U.S. because of the availability of testing, so I can't speak to the entire assessment across various genetic and racial profiles.

DR. GULICK: Dr. Fish.

DR. FISH: It was mentioned in the presentation that coadministration of didanosine and atazanavir should be separated in time. Is it just a coadministration buffering issue, because in the information that we were given, it looks like the impact on atazanavir levels is substantial and that the PK data, when they are given in the same patient, although separated in time, and how much time is necessary since they are both once-a-day drug deliveries?

DR. SCHNITTMAN: The effect is purely an antacid effect, buffering effect, and with a two-hour separation, there is no decline in concentration.

DR. GULICK: Mr. Sharp.

MR. SHARP: I was wondering about adherence studies. I mean this is a once-a-day drug, but I think we need to look at adherence. I wonder what you have done.

DR. SCHNITTMAN: Adherence, as you say, is a critical question. The problem with the blinded pivotal trials is that we have dummy pills, placebo pills, et cetera, so that, in effect, for those studies, one has the same number, and one cannot evaluate adherence per se on that.

We do, though, now in our experienced patient studies and future studies where we don't have the blinded situation, actively controlling, capturing that information for adherence and compliance.

MR. SHARP: Are you going to be doing interaction studies with tenofovir and nevirapine?

DR. GIORDANO: The tenofovir one, in fact, we have recently completed, but that data is currently under FDA review, and nevirapine is a planned study that will occur very soon.

MR. SHARP: When will the methadone studies be completed?

DR. GIORDANO: As I said, it is currently underway. I suspect that we should have some preliminary information hopefully by the end of this year.

DR. GULICK: Dr. Kowey.

DR. KOWEY: I have two questions actually. One has to do with clinical, and one preclinical.

Obviously, in the 076 study, we are used to seeing doses of drug given which are much higher than the doses that are recommended for clinical use, and I suspect that the reason you didn't do that, at least in the repetitive dosing scheme, was

because of the fear of inducing hyperbilirubinemia in a normal volunteer population.

But if it's true that the metabolite doesn't have much of an effect on HERG, and if it is true that the metabolites are not important, why not do a large dose, single study in QT looking at values in Cmax?

DR. LAWRENCE: I think a partial answer to that is that although the 800 mg dose is twice the 400 recommended dose, the exposures are more than twice, so we at least achieved exposure levels that are unlikely to be encountered by the 400 mg dose or the boosted dose.

Now, as far as the safety margin, that study maybe doesn't provide the 5- or 10-fold margin that you would like, but I think looking at the data in toto, I think it is reasonable to conclude that the effect is negligible on QT.

DR. KOWEY: Well, I don't want to get in an argument with you now, because we will do this later, but I think that last statement we need to flag.

The second question has to do with the preclinical models. If I read the documents correctly, you looked at action potential duration

in a Purkinje preparation and you looked at HERG, and you looked at IKs, and that's it, that was your preclinical package? Is there anything else that I missed?

DR. LAWRENCE: As far as screening for QT effect, that's right. Our standard paradigm is to screen for those assays to see if a signal is present to do a dog study, to also look for a signal, and if any of those studies, a signal is present, then, we do the extensive sort of ECG evaluation that was done in 076.

DR. KOWEY: But you don't do any other preclinical work?

DR. LAWRENCE: Generally not.

DR. KOWEY: We will get to that later.

DR. GULICK: Just to let the committee know, I am going to let people who haven't had a chance to ask questions first before I go back to people a second time.

Dr. Illingworth and then Dr. Sherman.

DR. ILLINGWORTH: A couple of questions. One is the 10 patients who had values over 10, did they all have Gilbert's syndrome underlying?

DR. GIORDANO: They were not specifically tested for their genotype. Most of those patients

had other concurrent events, such as intercurrent hepatitis, either A or C, but they were not genotyped, so I don't know the answer to that question.

DR. ILLINGWORTH: You haven't done any testing in normal volunteers with Gilbert's syndrome to see whether they had a much bigger rise in bilirubin?

DR. GIORDANO: We have done genotyping in our Phase I program and our Phase II program, and as a general rule, patients who have the genotype which is consistent with Gilbert's will experience average higher bilirubin levels than those who do not.

DR. ILLINGWORTH: My second question concerns the lipid modifying effects. Have you looked at other markers of vascular disease, such as high sensitivity C-reactive protein to see whether this drug does not raise CRP where others do?

DR. GIORDANO: In the program to date, we have not looked at high sensitivity C-reactive protein. We have assessments such as those planned in some of our specialty studies that are ongoing in the III-B and Phase IV program.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: Thank you. The first question actually follows nicely on that one related to the EGT polymorphisms. Do you have any data where you can show the comparative levels of those patients that you sampled of bilirubin elevation?

DR. GIORDANO: Yes. The question was do I have data on bilirubin levels as related to genotyping, and I think slide 4N1 gives us some data.

[Slide.]

DR. GIORDANO: This is an illustration of the bilirubin level by concentration and then the 6/6, 6/7, and 7/7 with the 7/7 reflecting the Gilbert's genotype. You can see the trends where there is higher bilirubin levels at any given Cmin as the patient has two genes, the 7/7, which is the Gilbert's.

DR. SHERMAN: So, there was little effect on the 6/6s.

DR. GIORDANO: There is much less effect on the 6/6s, yes, 6/6s representing, as you know, what most of the population has.

DR. SHERMAN: You mentioned antacids

affecting presumably absorption. Do you have any data on that?

DR. SCHNITTMAN: The absorption of atazanavir is very dependent on low pH, so antacids could have an impact. At this point, we did do analyses to look at the patients who may have been taking antacids in the program, demonstrate neither a safety nor efficacy difference in those, and we do recommend that there is separation, just as there would be with didanosine of approximately two hours for antacids.

DR. SHERMAN: What about PPIs>

DR. SCHNITTMAN: PPIs and H2 blockers have more prolonged effects. We have not yet studied that, and that is an important drug interaction study that we need to do, and we will do.

DR. SHERMAN: I will ask one last one. This one actually is for the agency reviewer.

DR. GULICK: Can you speak up, Ken?

DR. SHERMAN: This question is for the agency reviewer related to the ALT abnormalities. I saw one slide that suggested that although there was not an increase in Grade 3/Grade 4 ALT abnormalities, compared to nelfinavir, it appeared there was overall an increase in all ALT

abnormalities, Grades 1 through 4.

Is that correct and was that statistically significant?

DR. MARCUS: Yes, that's correct. I believe that it reached statistical significance, but I would have to check and get back to you with that.

DR. SHERMAN: The follow-up to that would be is it attributable based upon known associations with underlying viral infection or is it thought to be primarily drug related?

DR. MARCUS: It is not associated with underlying viral, if you are referring to hepatitis B or C co-infection, the incidence of hepatitis B and C co-infection were similar between atazanavir and nelfinavir. Whether it is related to atazanavir or not, I would say that one might reasonably that it is a drug-related effect, however, it did not appear to result in an increased incidence of severe elevations or discontinuations.

DR. SHERMAN: I think that is also something that perhaps needs to be discussed later because lower levels may still contribute to significant long-term toxicity.

DR. GULICK: Dr. DeGruttola.

DR. DeGRUTTOLA: I had a question on the calculation of the mean difference, mean change in viral load from baseline. How are assays that went below limits of detection handled in those comparisons?

DR. LaBRIOLA: Dominic LaBriola, Biostatistics, BMS.

We actually imputed a value of one less than the lower limit of quantification in the calculations. So, if the limit of quantification was 400, we would impute a value of 399 for calculating means.

DR. DeGRUTTOLA: So, you didn't use any censored data methods for those?

DR. LaBRIOLA: No.

DR. DeGRUTTOLA: I had a question about the ALT elevations that appeared to be more common in the atazanavir in one study, the 043 study, but not in two other studies. It was mentioned during the presentation that that 043 study was an outlier. I was wondering if that was based on some statistical evaluation of heterogeneity across studies, and I was also interested in whether that comparison of atazanavir to lopinavir/ritonavir was

significant for the ALT elevations in 043.

DR. GIORDANO: I was using the word outlier in the generic sense in that the frequency for lopinavir/ritonavir was much lower than we had seen in any of our other comparator trials in our program, and the 6 percent for atazanavir, we looked very closely at those cases, and 6 of the 8 were associated with other events, and it resolved to normal while continuing to take atazanavir, so do not think that that reflected a potential hepatic signal.

With regard to the statistical question, we did not routinely perform statistical tests on percent ALTs.

DR. DeGRUTTOLA: One final question. for all of the virological response analyses where you are looking at percent below 400 or below 50, were all of those done with non-completers equal failure?

DR. SCHNITTMAN: The intent-to-treat analysis were all non-completer equals failure, correct.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: Two brief questions. You showed us some data that suggested that the lipid

effect of PK-boosted atazanavir was more favorable than the Kaletra arm, but do you have any direct comparison of atazanavir unboosted to boosted in terms of whether the effects that were seen unboosted are attenuated at all when combined with ritonavir?

DR. GIORDANO: We don't have any direct head-to-head data in which a naive patient population was treated with either atazanavir or a boosted atazanavir with ritonavir to make that direct assessment, only the comparative data from 043.

DR. MATHEWS: How about across your studies in terms of the magnitude of the changes in LDL?

DR. GIORDANO: We have not conducted those assessments again because the studies reflect very different patient populations. There were experienced patients who came from perhaps five or six different regimens, went on to then five or six different regimens on the 045 and similar things on 043.

DR. MATHEWS: That is obviously a big question for the treatment-experienced patients once this drug is approved.

The other issue relates to exclusions from the registrational trials for liver dysfunction. What was the ALT cutoff for exclusion?

DR. GIORDANO: Greater than 3-fold upper limit of normal.

DR. GULICK: Can you repeat the question? I am not sure everybody heard.

DR. MATHEWS: The level of exclusion for ALT from the registrational trials, you said was greater than 3-fold. The question is what experience is there with patients who have more severe liver injury, and do we know anything about what their risk of further hepatotoxicity might be in groups that were excluded from the registrational trials, perhaps from the expanded access program?

DR. GIORDANO: We don't have large additional experience with patients who entered studies with ALTs or ASTs greater than 3-fold upper limit of normal to address that question. The expanded access program has more liberal entry criteria, but we don't yet have sufficient data to make any strong assessments.

I can parenthetically add that we have not identified any problems, but I think the experience

needs to be extended.

DR. MATHEWS: The reason I asked that question besides the obvious one that they were not studied as much related to this phenomenon which is fairly common and not something that I would anticipate would be a bigger problem with atazanavir, but the flare of liver injury that is often seen in patients who initiate combination therapy with a protease inhibitor in the setting of active hepatitis C or other liver disease.

The clinical problem, of course, always is how do you know what that flare is due to, is it due to hepatotoxicity of the drug, one of the drugs, is it due to immune restoration. I am not saying that this a problem specifically for this drug, but it points out a generic problem in the setting of elevated bilirubins, which most of these patients may have.

DR. GIORDANO: I would like to say one or two things and then perhaps Dr. Sulkowski can add a few comments.

One is overall, the frequency of transaminase elevations in the program was no different from comparators, and our population was quite rich for hepatitis C co-infected patients, 12

to 20 percent.

Your point is one which I would also ask Dr. Sulkowski to comment on with regard to how one might differentiate the two groups.

DR. SULKOWSKI: Mark Sulkowski, Johns Hopkins University.

I think you have raised a very good point and one that we have been keenly interested in, in the Johns Hopkins HIV cohort. That is the fact that in clinical trials, patients are generally selected, and that is not necessarily true just of atazanavir, but other PIs, as you point out.

In looking at our clinical experience, in a large cohort of patients enriched with hepatitis C, as well as other liver problems, such as alcohol use, we have, in general, noticed higher rates of Grade 3/4 liver injury.

I would not anticipate based on the data obtained in these registrational trials that that experience would be any different with respect to atazanavir compared to the other PIs we have looked like in our experience.

I think the second point you raise, which is how do you determine what is the etiology of event, remains a very vexing one, and one that is

difficult in clinical practice to often attribute the etiology.

Sometimes we find that there are other explanations, such as hepatitis A or B. Sometimes there are issues related to nucleoside analogs such a mitochondrial injury, and sometimes we can attribute it directly to the PI, but it is a difficult situation which requires clinical input.

DR. GULICK: I have Dr. Sun, then Dr. Washburn, then Dr. Remmel.

DR. SUN: I have two questions. The first relates to predictability of response particularly in treatment-experienced patients, because clinicians are using the available resistance tests more and more, and the question is, have you analyzed the response particularly in Study 043 versus genotype and phenotype, and how do you respond to the FDA's suggestion that a breakpoint might be in the 2- to 6-fold range for phenotypic fold change.

Another way to ask the question, I guess is, how would you expect resistance data to be reported out in some of the commercial tests that are currently available? That was one question.

DR. GULICK: Do you want to take one at a

time?

DR. SCHNITTMAN: The first question deals with predictors of response in the treatment-experienced patients. I would like to put up a slide 2J2 for you to see.

[Slide.]

DR. SCHNITTMAN: This is from the 043 study. We are looking here at Week 24 response rates by patients done in both overall and by different resistant subgroups. The resistant subgroups include PI sensitivity, whether or not there was one or more prior PIs, and whether or not there was nuc mutations present.

As you can see in the 043 data, that atazanavir has an enhanced response rate when the PI phenotype is less than 2.5 times control EC50, also when there is one prior PI, it is enhanced, but it does not appear to be a significant effect on prior nuc mutations.

Let's now look also to extend this, what we have done on 045 to try to understand this, as well, and this will be slide 2K2.

[Slide.]

DR. SCHNITTMAN: Here, we are looking at the same proportions in response, and we are

looking again here at effect of PI and nuc mutations and PI sensitivity. Here, we have three arms just to remind you again.

In green is the atazanavir/ritonavir arm. In blue is atazanavir/saquinavir, and in orange is lopinavir/ritonavir. As you can see on the left is the overall responses that are equivalent for atazanavir, ritonavir, and lopinavir/ritonavir.

We see an enhancement of response by PI phenotype less than 2.5, by having fewer than 4 PI mutations, and really no significant effect with nuc mutations. You can also see that the curves are pretty much the same for the two boosted regimens.

I do want to take this opportunity to have Rich Collono describe some of the genotypic changes that we see.

DR. COLLONO: Good morning. Rich Collono, BMS Virology.

What I would like to show you is just an analysis that we have done previously in analyzing 952 clinical isolates that were both susceptible and resistant to other PIs to try to understand if we can predict where atazanavir could be placed in terms of susceptibility.

[Slide.]

DR. COLLONO: In this slide again, just a very simple analogy which one would expect to see for most PIs, but again holds true also for atazanavir, that as you become resistant to more PIs, you start to lose susceptibility to atazanavir.

So, if an isolate is resistant to one to two PIs regardless of the PI, the specific PI, we retain approximately 86 percent of those isolates will still maintain susceptibility to atazanavir. That goes down as you become more cross-resistant, such that when you are resistant to three or four PIs, you have approximately 25 percent of those isolates still being susceptible.

Let's go to A16.

[Slide.l

DR. COLLONO: We have done a genotypic analysis of those 950 or so isolates trying again to understand correlations of the presence of an amino acid substitution with susceptibility to atazanavir, and the mutations that Steve has spoken about, PI mutations, we are referring to 14 amino acids that we have identified that correlate strongly with loss of susceptibility to atazanavir.

Now, we have gone through this analysis and found that no single amino acid substitution is predictive of lost susceptibility, nor do we find combinations of one or two that are susceptible, but if you get an accumulation of any five of those or more, that correlates fairly strongly with loss of susceptibility to atazanavir.

That is demonstrated on A18, the final slide that I will show you, the correlation with number and loss of susceptibility.

[Slide.]

DR. COLLONO: In this bubble chart, the size of the bubble is reflective of how many data points are at that particular spot, so the bigger the bubble, the more data points there versus a small bubble.

As you can see, along the bottom, on the y axis, we have number of Q mutations, number of these 14 Q mutations. In yellow, right along that axis, we have the mean EC50s that we obtained for that population of isolates, but as you can see, a gradual increase in resistance levels to atazanavir as you accumulate those mutations, and depending if you use a cutoff of 2.5 or 3.0, it looks like the breakpoint is approximately having 4 or so of those

mutations present.

DR. SCHNITTMAN: We see the importance of genotypic and phenotypic mutations now in allowing the clinician to make better decisions about which patients to treat and how to treat them is quite clear.

As a final comment, I would like to ask Dr. D'Aquila to make a comment on his impressions of this particularly as these are becoming more and more incorporated into the IAS and PHS treatment guidelines.

Rich.

DR. D'AQUILA: I am Richard D'Aquila from Vanderbilt.

I think the standard of care now does include antiretroviral resistance testing whenever a regimen is failing. This has been promulgated by the IAS-USA guidelines from 2000, as well as the DHHS guidelines.

There are new revisions to the IAS-USA guidelines that are in press that will further suggest additional situations where genotyping might be useful including screening before a first regimen in many cases.

I think because this is standard of

practice, we will be able to choose patients for whom atazanavir would be likely to succeed.

I would expand my answer a little bit to address what Dr. Sun asked. I think some of the genotypic criteria can be suggested from these data, and I am sure as we have seen with other protease inhibitors, we will continue to evolve those criteria.

I think the genotypic criteria will improve with increasing use starting with what we heard today. I think the phenotypic resistance cut point at present is probably going to be something around 2.5-fold, but again, I think further data would be helpful to see whether particularly if the drug is ever used with ritonavir boosting, that cut point might go up.

DR. GULICK: Dr. Sun, you had another question I think.

DR. SUN: The second question is related, which is in your analysis of the virologic failures from your various clinical trials, have you analyzed the pharmacokinetics in those patients especially given the fact that there is a fairly large variability in PK, particularly in HIV subjects, particularly around Cmin, and that might

account for a substantial part of the failures that you can't attribute just to phenotypic analysis.

DR. SCHNITTMAN: We have not selectively analyzed the pharmacokinetic parameters in those subjects who have failed. In fact, when one goes back and looks at these patients, many of the reasons for failure have to do with adherence compliance or other issues that really have no bearing on what the actual absorption of drug is.

It is really a complex multifactorial process that leads to failure of patients in these trials, but it is certainly a good point.

DR. GULICK: Dr. Washburn and then Dr. Remmel.

DR. WASHBURN: My question is about the hyperbilirubinemia. If I am remembering correctly, I think trimethoprim sulfamethoxazole is occasionally capable of causing hyperbilirubinemia, and I was wondering if any effort has been made to look to see whether concomitant trimethoprim sulfamethoxazole use may have played into the degree of hyperbilirubinemia seen in these studies.

DR. GIORDANO: As you can imagine, a very large percentage of the patients may have been and were taking trimethoprim sulfamethoxazole in our

studies, but we don't have any data to indicate that they had higher bilirubin levels compared to those not taking it. We didn't conduct a specific analysis of that question.

DR. GULICK: Dr. Remmel.

DR. REMMEL: I wanted to follow up a little bit on concentration relationships which you have got a drug with an AUC variability of 20-fold at the 400 mg dose, and did you do any studies looking at concentration relationships with bilirubin levels other than you presented something with Cmin, but perhaps Cmax or the average steady-state concentration might be better tools in that sense.

DR. GIORDANO: In addition to the work done with phenotyping, which is obviously a host factor, we have looked at AUC and Cmin and a variety of pharmacologic parameters, and in general, higher concentrations are associated with higher bilirubin levels, not just the Cmin, but also the AUC as you indicate.

DR. REMMEL: My second question was about the metabolism, which is a little bit sketchy in the report that we received. There wasn't even, you know, structures, and that sort of thing.

Could you fill us in on what are the metabolites, what are the percent of metabolite formed, and what are the enzymes responsible for the metabolism?

DR. SCHNITTMAN: Dr. Grasela will come forward to review the metabolites and their properties. As he is coming up, I will just mention that the three major metabolites there, which are all under 20 percent, none, by the way have anti-HIV activity, and Dr. Grasela will review for you what the specific CYP pathways are.

DR. GRASELA: Can you show slide 13D1, please.

[Slide.]

DR. GRASELA: This is a complicated slide that I will walk you through. In the circulation, atazanavir, approximately 54 percent of the components in plasma are atazanavir. There have been 16 metabolites that have been identified in humans and in animal species studied, 8 of those are in plasma.

Of those in plasma, only 3 metabolites are greater than 3 percent of total plasma radioactivity, and those metabolites are shown on this slide.

The metabolites are generated by a series

of oxidative processes. The specific PE for 50 enzymes that may be associated with those have not been completely worked out. The first metabolite is BMS-419, the structure is shown here. It represents between 14 and 20 percent of plasma radioactivity. The Cmax value is 0.27 micromolar. It represents about 14 percent on an AUC basis.

The second metabolite is 160, the structure is shown here. It is 12 to 18 percent of plasma radioactivity, Cmax is 0.54 micromolar with steady-state AUC ratio of metabolite to parent of about 29 percent.

The third metabolite, this is a postulated structure for that metabolite, is about 14 percent of plasma radioactivity.

As Dr. Schnittman had indicated, these are not active against HIV. 419 has not been shown to inhibit any of p450 enzymes. 160 has not been shown to inhibit any of the p450 enzymes either. 2C19 has an IC50 value of 4.9 micromolar, which is 10-fold that of the Cmax value.

DR. REMMEL: There was also mention of a glucuronidation as a potential pathway, and is that catalyzed by UGT 1A1, or is the compound a substrate for UGT 1A1?

DR. GRASELA: Atazanavir is not a substrate of UGT 1A1. There are some glucuronide components in the urine, and they have been associated with these metabolites.

DR. GULICK: Anyone who hasn't had a chance to ask a question on the committee? Okay. I have a few and then I am going to go back to the people who would like to ask one more question.

The first is virologic response on 034. While it is difficult to compare responses across studies, the percentages less than 50 really are quite different from other studies that we have seen, particularly for the efavirenz control arm.

Could you comment on those results?

DR. SCHNITTMAN: You are right, it is difficult to compare across studies. Clearly, for the less than 400 copies per ml, the response rates that we are seeing here were comparable to that seen in the DMP-06 study, which is in the efavirenz label.

Regarding the less than 50, we have done extensive analysis looking at what are some of the possible contributing factors to the lower response rates that we are seeing there. These included several.

One was study conduct. As I mentioned earlier, patients that switched nucleosides were counted as failures, which impacted significantly. In addition, we utilized a growing amount in many of the countries of 1.5 assay for the amplicore versus the 1.0. For those who may be aware of it, the 1.5 is a much more sensitive assay, picking up non-clade B's, but even for clade B's, it raises the RNA approximately 0.3 log, which can lead to higher RNA values than people would have measured in previous studies.

In addition, we utilized PPT tubes, since this was a multi-national study, that we wished to limit risk to people working with the specimens, but we used these tubes, so they didn't have to open them. They shipped these as gel separator tubes after they were spun down frozen in situ.

What happens using the PPT tubes, there is sometimes greater release of RNA from the cellular elements that could raise the level of RNA.

So, we can't give a specific contribution to each of these things, but we think together they may have contributed.

Can we now show slide 2A2.

[Slide.]

DR. SCHNITTMAN: We did look at the question, though about the variability around the 50 copy per ml cutoff. As I know many of you are aware, this is a thing that has been looked at and examined by the ACTG and other investigators in terms of the variability around that 50 cut point.

We looked at response rates on the TLVR analysis for 400, 200, and 50. As you see, the 400 and 200 response rates are very close to each other, meaning that most of the failures are occurring in the 200 to 50 range.

The next slide.

[Slide.]

DR. SCHNITTMAN: On the histogram, this shows you quite specifically that most of the RNA values that are occurring here are between the 50 and 200 range, but very importantly, notice that the pattern is the same for both atazanavir and efavirenz, so the effect is really not treatment specific.

DR. GULICK: Thanks. Regarding Study 043 in experienced patients, can you review again what the entry criteria was? Specifically, it is failing one PI, but what was the definition of failure?

DR. SCHNITTMAN: They need to have at least 12 weeks experience with a rebound of at least a log above their baseline to enter, as well. They could also have had --we did not exclude people who also had a non-nuc failure, so they could have had PI plus a non-nuc.

DR. GULICK: Did I correctly pick up that only 56 percent of the patients at baseline had any PI resistance on that study?

DR. SCHNITTMAN: About half the subjects had nelfinavir resistance looked at alone.

DR. GULICK: And that follows up to my next question. So, if people failed one PI, but they could have taken other PIs prior to that, is that right?

DR. SCHNITTMAN: That is correct. They could have taken it and come off of it for intolerance or other reasons, and we had no way of controlling to what extent they took it and for what reasons, but theoretically, the intent of it was just to have a single failure of PI, but they could have taken more than one.

DR. GULICK: Do you have a listing of what the protease inhibitors were that people took?

DR. SCHNITTMAN: We will dig that up.

This is the prior PI usage in 043.

Nelfinavir was the one, by the way, of greatest usage, not surprisingly.

DR. GULICK: That is what I was interested in, and the percentage on nelfinavir roughly?

DR. SCHNITTMAN: It was probably three-quarters, I think it was close to three-quarters of the patients with indinavir then coming behind that.

DR. GULICK: A last question about the 043 study. Maybe I missed it, but did we see the resistance patterns for people who failed in terms of nucleoside resistance?

DR. SCHNITTMAN: What I showed there earlier was in terms of number of nuc mutations, what it looked like, and the presence or absence did not really predict whether those patients were going to be responders.

DR. GULICK: Maybe I am not being clear. At failure, we heard a lot about what the PI resistance looked like, but unless I missed it, we didn't see what the nucleoside resistance was in people that experienced failure.

DR. SCHNITTMAN: I am not sure if we have the distribution of the nucleoside resistance.

DR. GULICK: I am interested because you would expect to see lots of 3TC resistance, but clearly, other studies have shown differences among arms in terms of the amount of 3TC resistance.

DR. COLLONO: This looks at all the resistant isolates again, at atazanavir-resistant isolates, and what happened in terms of the nucs. I hope this is what you are asking.

In the naive patients, again, for 007 and 041, you had 12 that failed on atazanavir, we had one that also failed on the nucs, which happened to be this case, BDDI-D14, and then 3 out of the 4, 6 out of the 7 in naives, and in the experienced populations, again, you can see the numbers.

The interesting thing in the experienced populations that many of those failures actually started on baseline resistance to start with, so you can account for a number of the atazanavir resistance by the fact that they are already resistant.

DR. GULICK: Thanks. My last question is for both the sponsor and the agency, and it's about lipodystrophy. We heard it stated that there is no effect of these lowered lipid levels on the occurrence of lipodystrophy, but I would like to

ask what definition was used and how is that assessed by the investigators?

DR. GIORDANO: I can start if you would like. Lipodystrophy was collected passively on case report forms without specific criteria for diagnosis. We did use the ACTG guidelines for how one may assess lipodystrophy as a tool which investigators could use, but there was no specific criteria by which a lipodystrophy diagnosis could be made.

That said, we included broadly any term that might be reasonably thought to represent lipodystrophy, so fat redistribution, fat lumps, sometimes weight gain, weight loss, et cetera.

DR. GULICK: It's 12:30. Three other people have asked to have brief questions, so we will allow those.

Dr. Kumar, then Dr. Wood, and then Mr. Sharp.

DR. KUMAR: I wanted to ask the effect of unconjugated bilirubinemia in pregnancy, specifically, whether you could postulate whether there could be any of the clinic [?] tests done for the unborn child?

DR. GIORDANO: I am sorry. Could you say

that one more time?

DR. KUMAR: I am interested to see whether you have any information or whether you could help me understand the effect of the elevated unconjugated bilirubin in pregnancy, specifically, whether there may be a risk, a chronic risk to the child.

DR. GIORDANO: There were patients who were pregnant on atazanavir trials, not very many pregnancies continued on atazanavir through delivery, however, based upon the biology of elevations in bilirubin observed on atazanavir, one would not expect that those levels of bilirubin would pose any difficulty for the fetus.

I would like one of our consultants, Dr. Wolkoff, who is here, and who is a bilirubin expert, to give us some comment, as well.

DR. WOLKOFF: Hi. I am Allan Wolkoff from the Albert Einstein College of Medicine.

That is a good question, but the levels of hyperbilirubinemia in the patients treated with the drug were rather modest, and it's all unconjugated. Other studies looking at transfer of bilirubin across the placenta have shown that it transfers from baby to mother, but really minimally the other

way.

There are also case reports, for example, a case of Crigler-Najjar syndrome type 2, which for our purposes we could think of as a bad Gilbert syndrome, because there is a greater reduction in UGT 1A1 activity.

In that woman who was pregnant, she ran bilirubins of 8. She had normal delivery of child. That has been the experience with other patients. There is no problem with delivery of normal children in patients with Gilbert's syndrome, as well.

DR. GULICK: Dr. Wood.

DR. WOOD: This data was not presented by the FDA or the sponsor, but it was in the sponsor's brochure, specifically Table 8.3, that summarizes the adverse events in the pediatric population.

One of the things that I noticed is that approximately 48 percent of the AEs have to do with cardiac issues in terms of either bradycardia, prolonged QT was actually seen in two patients. That is on page 157.

I was wondering whether or not there was any correlation between these adverse cardiac events in terms of analysis of pharmacokinetic

levels. I know that a dose has not yet been identified, but this is approximately 48 percent of the pediatric patients having adverse events related to EKG abnormalities. That is much higher than what has been reported in the adult studies.

DR. SCHNITTMAN: The PACTG has a fairly unique approach in adverse events, and by the way, these adverse events were collected even for a first-degree heart block was considered an adverse event as an isolated thing to count even though it was associated with no symptoms.

Overall, though, my understanding is that that was not an issue. We do have Dr. Rick Rutstein, who is the PI of that study, who can share with you his impression about the safety evaluation particularly on ECGs with the 1028 study.

DR. RUTSTEIN: Rick Rutstein from Children's Hospital, Philadelphia.

We used a very conservative rating of PR intervals and QTc based on age-adjusted limits, so that if you are 2 percent above, if you fell in the normal 2 percent elevated PR range for normals, you are considered an abnormal and an adverse event, so we have a high rate of first-degree PR elevations.

None of them was significant. Two patients came off based on PR elevations before we had written a protocol amendment to specifically look at that. We had started the protocol before the initial EKG abnormalities had been available from the adult studies.

Since we have done that, no patient has come off based on PR changes, no patient has had any symptomatic changes, and we have done holter monitors and everybody has had a mildly elevated PR interval while on study, and they have been normal, as well.

DR. SCHNITTMAN: Thank you, Dr. Rutstein. We have been very aggressive in doing a very similar ECG type program as we did in adults.

DR. WOOD: That is a very helpful clarification, thank you. I had a second question, and that was in terms of the drug interactions and recommendations. Particularly given the fact that the patients who had the most intense levels of elevated bilirubin also tended to be co-infected with hepatitis A, B, or C, are there any plans to do any studies examining atazanavir in patients who are taking ribavirin and PEG interferon, or have you all done any studies?

DR. SCHNITTMAN: Ribavirin is definitely on the plans. It was my impression, though, that overall, bilirubin elevations were not significantly different in co-infected patients.

DR. GULICK: Mr. Sharp.

MR. SHARP: I am wondering about--going back to the absorption issue again--does high fat food have more of an effect on absorption than just a regular diet, and if so, is the FDA planning to put a special warning in the labeling? And I have another question.

DR. SCHNITTMAN: Food of all types, both light meal and high fat meal, enhances the absorption and the concentrations of atazanavir, as well as diminishes the coefficient of variation, so that is why we recommend food in a general sense, and there is no restriction.

MR. SHARP: So, there is no difference.

DR. SCHNITTMAN: In single-dose studies, it looked like light meal was a little better than high fat meal, and multi-dose, vice versa, but there is no substantial difference.

MR. SHARP: We saw the data on the contraceptives, but I wondering, it wasn't really significant, but it is an issue, and I wonder if

there is going to be a specific warning about contraception coadministration.

DR. BIRNKRANT: We can't comment on labeling at this point in time, as we haven't made our regulatory decision yet, but labeling in general reflects data submitted in an application.

DR. GULICK: Last-minute burning information-based questions are welcome.

Dr. Illingworth.

DR. ILLINGWORTH: Just one question concerning the absorption of the drug. Is it dependent on fat absorption to be absorbed? It is lipid soluble? Is it absorbing the caller [?] microns How is it absorbed?

DR. GRASELA: We don't have specific data regarding transport of the drug using caller microns to go through. We presume it is passive diffusion. We do have data at higher doses in which the exposure does not increase in proportion with the dose, suggesting is it dissolution-rate limited in its absorption.

DR. ILLINGWORTH: If you do a postprandial lipemia study given the drug, is it in caller microns or not?

DR. GRASELA: We don't have data

specifically about that.

DR. GULICK: Dr. Schnittman, you have the PI data?

DR. SCHNITTMAN: The question that you asked before, we are putting up the slide.

[Slide.]

DR. SCHNITTMAN: This is from the 034 study in looking at virologic failures, but I want to focus on the bottom portion of the slide, which is the genotype. Number one, you see the I50L, which is the PI marker there. We have the K103N, not surprisingly greater on efavirenz, but we also have the distribution of nucleoside didovidine [ph] mutations, as well as the 184, and as you can see, they are comparable for both atazanavir and efavirenz.

DR. GULICK: Does that mean that about half of patients who are able to be genotyped had no mutations at all, they failed with wild type?

DR. SCHNITTMAN: That's correct.

DR. GULICK: Dr. Fish, you have the honor of having the last question.

DR. FISH: My question relates to our cover mentions that the atazanavir is available in the powder formulation, so I presume that is for

the pediatrics.

Is there data, use of this formulation in adults, for example, those that might have G-tubes, swallowing difficulties, et cetera?

DR. SCHNITTMAN: No, at this point, there isn't. An important issue is that we have not demonstrated bioequivalence of that formulation in adults. That work is going on right now.

DR. GULICK: Let me go ahead and stop us there. We will have time for additional questions within the discussion period, but that's a good start. It's 20 of 1:00, so let's break for lunch and we will resume at 1:30.

[Whereupon, at 12:40 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

AFTERNOON PROCEEDINGS

[1:30 p.m.]

DR. GULICK: One announcement. If people could remember about the surveys, the conflict of interest surveys, please fill them out, complete them, and there is a box at the registration table where you can leave them. That would be appreciated.

There was one issue in the question and answer period that we wanted to follow up on, which was the incidence of LFT abnormalities.

DR. SIGAL: Yes. Thank you. I just want to make sure people leave with a clear impression of the data on the LFT abnormalities because the discussion focused on one study 007, and we want to make sure in the totality of the whole clinical experience, you have what we have in terms of the impression of the data.

Michael Giordano.

DR. GIORDANO: First, I would like to show a slide among co-infected patients to break down by study the frequency of Grade 3 elevations in transaminases.

[Slide.]

DR. GIORDANO: You can see that although

more frequently elevated transaminases were observed among those who are hepatically at risk, those with co-infection, with every comparison to atazanavir, the frequency of those elevations was either equivalent or slightly less.

I showed the composite slide, which is the overall frequency, so 10 percent of patients co-infected with hep B and C, who received atazanavir, had a Grade 3-4 elevation in hepatic transaminases, 11 percent on the comparator. When they were not infected with hep B or C, the frequency was 3 percent for atazanavir for a roughly 3-fold ratio, whereas, the ratio on comparators was 11 to 1.

Also, with regard to the frequency of transaminase elevations across the entire program, when we look at Grade 3-4 elevations in particular for the Phase III programs, the frequency is comparable, and I think I showed you those numbers for the 034, the 043, and the 045 studies.

DR. GULICK: Could we have the lights down, so that we could read the slide. Sorry, Michael.

DR. GIORDANO: We can spend a little bit more time on this slide if you want. If you look at the top line, which is hepatitis B co-infection,

it compares the frequency in co-infected patients for atazanavir versus comparators, and you will see the general trend is that the frequency is less. For atazanavir versus comparator, which is then reflected in the overall frequency of 3-4 elevations, on the bottom graph, and that is the slide I showed in the core.

So, 10 percent of hep B co-infected patients, hep B/hep C co-infected patients experience a Grade 3-4, whereas, 11 percent of comparators, so the hepatic safety with regard to co-infected patients is comparable to that seen in comparators. When you build up to that number from the individual studies, you see the same trend.

With regard to liver function abnormalities of all grades, I think, as indicated in the presentation, when you look at all grades in the Phase II studies, 007 and 008 study, there was an increased frequency of low-grade LFT elevations, ALT, AST in 007 and 008, that was not observed in our Phase III program, neither in 034 or 043 or 045 studies.

So, I wanted to just make those points.

DR. GULICK: Thanks very much.

We are now going to begin the open public

hearing portion of the meeting, and we have had one person sign up to speak at the meeting. That is Rob Camp from the Treatment Action Group.

Rob, you can use the podium up at the front if you like.

Public Hearing

MR. CAMP: Thank you very much.

I would like to thank the FDA for allowing me to speak here today, and I would like to congratulate BMS on the amount of data that they have presented and the new data that they have presented today. It sort of makes my position paper that I finished yesterday at 2:30 really not very completely useful anymore because there is a lot of new data since yesterday at 2:30, but anyway, there are still a few points that I would like to make.

A number of community groups from around the country have signed on to the paper, and they would like me to say a few things.

First of all, we are happy, yet concerned, that the accelerated approval has been turned into traditional approval, partially because we feel that many of the studies, many of the questions that haven't been answered may not have to be

answered, and the sponsor can in one way or another not get around to them.

We hope that the FDA and BMS work together to answer the questions that a lot of people still have. We are a little concerned that the advertising restrictions that accelerated approval would have would not be lifted under traditional approval, and we really must stress that pharmacovigilance be an important part of the follow-up to this drug.

In any case, I was very interested this morning, someone from the panel mentioned that we can possibly eliminate some people who tend to get hyperbilirubinemia by genotyping, and if that is really the case, we can possibly, by eliminating those people, give more atazanavir to people, up the dose, and make this from a moderately potent PI into a very potent PI. That might be something worth looking into by eliminating people who would automatically tend toward hyperbilirubinemia, people who already have Gilbert's syndrome, for example.

The studies that still need to be done, I think all of the studies have already been mentioned this morning by the panel, and I would

just like to underline them, PK studies with methadone, H2 blockers, rifampin, statins, vibrates, ribavirin, efavirenz, nevirapine, tenofovir--I heard tenofovir was done, that's fabulous--fosamprenavir, saquinavir, both formulations, and pegylated interferon. Also, Jules just reminded me that we should have toxicity and safety also on some of these things especially with the hepatitis C drugs.

Long-term safety studies were also highlighted by the panel this morning and they are very significant and very important that they continue.

It was disappointing to hear that the lipid changes don't also make a better lipodystrophy profile. That really is disappointing. One thing that we would like to possibly see in the labeling is a clear definition of lipid profile versus lipodystrophy. Having a good lipid profile doesn't mean you won't get lipodystrophy. I think that is very important, especially for users of this drug.

I think clinical management, of course, as with all drugs, will be very important and if we can somehow really make this genotyping of

Gilbert's syndrome work, then the worries about the masking of hyperbilirubinemia won't be such an issue; in other words, if you go to your doctor and the high bilirubins are automatically assigned to atazanavir but maybe it is from something else that won't be seen because automatically it will be assigned to atazanavir. I would just like to underline the importance to not forget that.

So the etiology of bilirubins in the liver is still very important, especially probably with drugs like nevirapine that haven't been looked at together yet.

I'm curious, and you can answer this afterwards, but one question I had from this morning was the ddI used in the trials; was it the buffered ddI or was it another ddI and did it change according to trial. That might be interesting also in looking at the different results of some of the trials.

What are the effects on lipids of ritonavir-boosted atazanavir? I think that has to be clearly defined and clearly spelled out in the label. I think that the FDA has to really consider, and the advisory panel has to really consider, what they are going to put on the label

as far as if it is only atazanavir without ritonavir, then, what type of patient is it, and then with ritonavir, it is a different type of patient. I think those things have to be clearly defined before approval.

The adherence and compliance issue is a little bit worrying, not in the sense that once a day isn't easy, but in the sense that if someone does miss one day, that's a big window that is open without drug for 24 hours, that might be considered serious.

Little useful data has been generated so far for pediatrics, and we really hope that pediatric data is generated quickly.

So, that is more or less for the clinical part. I would like to read a short note from the Fair Pricing Coalition, as well.

They say that in this time of severe funding shortfalls at the state and federal levels, negotiations between BMS specifically and the Coalition of State ADAP Directors has stalled.

I am here to express profound disappointment at BMS's failure to negotiate serious price discounts and freezes in good faith with state and territorial ADAP Directors.

BMS's inaction will lead to the irreversible dismantling of ADAPs by forcing the programs to lower their financial eligibility, create barriers to needed medications through prior authorization procedures, and by the removal of drugs from ADAP formularies.

With people living longer and the continuing new infection rates, publicly funded programs are stretched to the breaking point. Under the current economic climate, we are clearly in a new era that demands a complete rethinking about the pricing of HIV drugs.

There has been nothing extraordinary about the cost of clinical trials required to bring these new drugs to market. Indeed, thanks to accelerated approval, development costs may be lower for many HIV drugs than for other drugs, while the duration of their use by patients can be greatly extended.

Thus, the price of atazanavir should be price and cost-neutral for ADAP, Medicaid, and private insurers.

Thank you very much.

DR. GULICK: Thanks. Could the sponsor clarify the one question about the ddI formulation that was used on the studies?

DR. SCHNITTMAN: Yes, ddI was used in 007, and that was the old buffered formulation. As we move to the experienced patient trials in which people selected the different nucleosides, at that point, EC had been approved and is being used in the studies.

DR. GULICK: Thank you.

That was the only person who signed up for the public part of the hearing. Is there anyone who didn't sign up who would like to make a statement at this point? Jules Levin.

MR. LEVIN: I just have something real brief to say. First of all, I thought this was a good hearing. I have been to every hearing since I started this work about eight years ago, every HIV drug hearing, and I thought that for the first time, the FDA did what I thought was a good job in my experience, and I also think that the company did a very good job in addressing a lot of the concerns.

The question was asked to me by some people, how come there was a public hearing today, is it because of all the issues, bilirubin, and so forth, or is it because the community met with the FDA and asked them to hold public hearings on

drugs, and I don't know the answer to that.

So, I thought that with short-term data, which is 48 weeks, 100 weeks data, is essentially short term, that the drug looks pretty good. I support the issues that have been brought up, bilirubin, and so forth, look pretty good.

So, I personally really support approval. I don't think you need me to say that because I think it's going to get approved. But I think the community would support this, too, so I think I can speak for the community in saying that, as well.

But what I would like to say is that I would like a longer term follow-up than 48 weeks and 72 weeks with regards to the concerns that we do have with regards to bilirubin and ALT elevations.

I would like to see longer term safety and toxicity follow-up from the company, as well as from the government to make sure that this gets done.

I still have some lingering questions about the LFT stuff. I understand that there was just some presentation, some data shown about how it doesn't appear as though there is an issue, but I would like this to be continued to be followed

particularly for people that have co-infection with HCV and HIV.

So, that is pretty much what I have to say.

DR. GULICK: Thank you.

Anyone else who didn't sign up who would like to make a public statement?

Okay. We will close the open public part of the hearing and go to the Charge to the Committee.

Dr. Birnkrant.

Charge to the Committee/Questions for Discussion

DR. BIRNKRANT: Thank you.

As we heard this morning, HIV--and we recognize this, the agency recognizes this--is more of a chronic disease at this point, and we are looking at it somewhat differently than we looked at it many years ago given that not only is benefit important as we review these clinical trials, but risk becomes even more important than it has in the past.

So, as you deliberate today, we will ask you to take into account the evaluation of the signals that were seen in the preclinical and the early clinical database.

So, with regard to the first question, the safety and efficacy of atazanavir, we would also ask you to comment on the hyperbilirubinemia that was seen and the data that were presented, as well as the effect of atazanavir on conduction, namely, PR and QT intervals.

With that, we would also like the committee to comment on the use of this drug in the populations that were studied and presented today, keeping in mind that the agency has not reviewed the efficacy data from 045.

If you feel as though 045 is crucial to your answer, then, clearly, include that and explain that as you respond to the various questions, but again I would like to emphasize we have not reviewed that data to date.

In addition, if you determine that this application should be approved, then, there are a series of questions that follow, namely, issues related to monitoring for LFTs, EKGs, should genotyping be done, et cetera.

So, as you answer that question, keep in mind those issues.

Please also keep in mind when you answer the questions the effect seen, as I said, in the

different populations, and how the resistance data plays into your discussion.

We also have a question related to additional studies that would be important for you to see and have the applicant conduct.

With that, I would like to move to the discussion of the questions if that is okay with the Chair.

DR. GULICK: Great.

Question No. 1 to committee: Do the efficacy and safety of atazanavir support its approval for the treatment of HIV infection? As part of the discussion, please comment on: treatment effects in naive and experienced patients, hyperbilirubinemia observed in clinical trials, and the effects of atazanavir on PR and QT intervals.

Let's take these one at a time. Let's start off with a discussion of the treatment effects seen in naive patients.

Who would like to begin? Dr. Mathews.

DR. MATHEWS: I could be very brief on that because that is the most clear-cut evidence, I think, that it clearly is active and it was compared to a very challenging comparator arm with

efavirenz-containing regimen, so I feel very comfortable with that answer.

DR. GULICK: Dr. Remmel.

DR. REMMEL: At the 400 mg dose, clearly, there was good effect with atazanavir, but I am concerned about the pharmacokinetic variability of the drug with the 20-fold range and Cmins, and percent coefficient of variation around the variability.

While the sponsor probably wouldn't want to encourage concentration monitoring, this is a major issue in terms of many of the protease inhibitors in particular, especially because they are all CYP3A substrates, and I think that we could see some benefit if that was to be done, but I would like to see some sort of indication in terms of how many patients who fell at the low end for the Cmins or area under the curve were actually failing and what is that component in terms of the efficacy of this drug.

So, that is my only major comment there. In terms of the experienced patients--

DR. GULICK: Let me hold you on that, and we will stick with naive patients for now. Then, we will come back to experienced patients.

Any other comments on the naive patient group or the data that we saw for naives?

DR. ENGLUND: I think the data they presented was quite convincing and that for the real world where we are working, I particularly working with adolescents where pill burden is absolutely, for my patients, the number one concern that they have, of course, it is our job to work on safety, but pill burden is incredibly important, the number of doses a day, and this drug offers equivalency in terms of many of the other parameters.

I am not worried about the effects of hyperbilirubinemia that have been presented so far although I think we should discuss this further later on, but in terms of the treatment effects seen in naive individuals, I think, yes, it is important and I think there is clearly a niche and that they have presented some good data to convince me that it would be a good thing.

DR. GULICK: Let me just say to the committee that at the end of the discussion of the first question, we will take a formal vote, so don't feel compelled to ring in if you know how you are going to vote already. It is not necessary to

do that, but thanks.

Other comments on naive?

Okay. Let's move to--half a comment from Dr. Fletcher.

DR. FLETCHER: Actually, I think these are probably just more some clarifying questions. In terms of the dosage forms that are being requested for approval, is the 100, 150, and 200 mg capsules or is it just 200 mg capsules, is it the powder, not the powder? I can't really tell from the information we have what the approval is actually being requested for, dosage form-wise.

DR. MARCUS: It's for the 100 mg, 150 mg, and 200 mg capsules.

DR. FLETCHER: The second question I have, it comes back to something earlier this morning, and that is the food effect on absorption. I am wondering, from the sponsor, I would just like to see a picture of what a recommended meal looks like--well, okay, a description of what a recommended meal looks like, how many calories, fat, if it could be translated into what does someone really have to eat in order to get the optimal absorption for the drug.

DR. GRASELA: In our single-dose food

effect study, we look at both a "light" meal and a high fat meal. A light meal is approximately 350 calories and approximately 25 percent fat, I believe. The high fat meal is approximately 950 calories and about 50 to 60 percent fat.

DR. FLETCHER: In terms of an effect on bioavailability, you see no difference between the light meal and the high meal in terms of atazanavir concentrations?

DR. GRASELA: In the single-dose study, the bioavailability was actually increased more with the light meal than the high fat meal. The variability was reduced in both meal types. When we did sort of a composite analysis following multiple dose administration, and it was confounded by the administration of saquinavir unfortunately, the high fat meal, light meal, were equivalent.

So, therefore, in our view, it's a wash, and in the clinical trials, it was given without regard to the meal type.

DR. FLETCHER: And that was answering my question, so in a study like 034, what was the recommendation, then, on the meal?

DR. GRASELA: My understanding is that it was to be taken with a meal, but it was not

specified.

DR. GULICK: Mr. Sharp.

MR. SHARP: As a treatment-experienced patient, I am concerned about approval of this drug in experienced folks. I am a little bit worried that--

DR. GULICK: Can I stop you just for a second? I want to stick with naive until we are done, and then we will pick up on experienced, I promise. In fact, maybe we will do it right now. Sorry. Go ahead.

MR. SHARP: So, continuing on. I am concerned that more studies need to be done looking at experienced folks, and some of those studies would be just looking at the combinations. We are on so many drugs. The pharmacopeia is just huge and people like me who have been on all the drugs and are continuing to take prophylaxis therapies and everything else that goes along, I am really glad that people could get effect from the drug with one protease inhibitor use. I think that is really important to distinguish.

But there are other studies that I think need to be carried out, and I am really concerned that if the drug gets full approval, as Rob said

earlier, I am concerned that some of the follow-up studies will not be done. So, I just want to make that point.

DR. GULICK: Dr. Fish.

DR. FISH: An area of concern, I certainly think the data looks good for both naive and with the concerns as we will get to in terms of the experienced patient population, but for either group, as we move towards treatment simplification, and we are talking about once daily therapy in that push, already there are clinicians who sacrifice I think the didanosine and empty stomach piece in the interest of doing it once a day, and we will not be able to do that with this particular combination.

So, special attention to use with didanosine in particular with atazanavir could cause potentially that treatment regimen to fail.

In terms of the patient-experienced population, I think the take-home message for me is that it has a niche, but I am going to use resistance testing to guide me, and I very much appreciated the genotypic information that was offered today in terms of helping me to guide that treatment decision.

DR. GULICK: Other comments on the

efficacy and the experienced population? Dr. Mathews.

DR. MATHEWS: There is a real dilemma, I think, facing the committee and the agency because if the agency has not reviewed the 16-week data on the PK-boosted regimen, and yet the data that was reviewed in experienced patients faces the treater with the decision of using a regimen which may have inferior virologic outcomes, but have a lot of advantages in terms of simplicity, tolerability, and so on.

So, it is not as clear to just say it's efficacious in the case of highly treatment-experienced patients based on the data that is reviewed and reviewable at this point. You could say that it's superior to placebo based on the comparisons that were done in that trial, but inferior to a regimen containing Kaletra.

What hasn't been talked about is what are the long-term consequences of using an unboosted regimen without atazanavir in terms of further accrual of resistance mutations and longer term significant virologic and then immunologic failure.

So, I think we need to discuss that more.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: This would be a question I think probably more to the agency. If the committee were to recommend approval for treatment-experienced patients, would the agency consider, in the dosing recommendations, the use of the boosted atazanavir/ritonavir dose, so the 300/100 mg regimen, or does the dosing really have to be constrained to the 400 mg, once daily, dose?

DR. BIRNKRANT: As of today, it would be restricted to the 400 mg dose. The PDUFA date, that is, the date by which a regulatory decision has to be made by law, is the 20th of June, so between now and then, there isn't that much time to review that additional data that came in late.

DR. GULICK: Just to point out, it puts us, as a committee, in a little bit of an awkward position because we are seeing evidence of activity, but it is not as good as a comparator arm, at the same time, we saw preliminary activity which hasn't been reviewed by the agency, which seemed to suggest similar virologic effects to a Kaletra-based arm.

In addition, the pharmacokinetics to support better drug levels and a better Cmin, when boosted with ritonavir, so I think I am seeing some

shaking heads, that we are feeling a bit conflicted about this point.

DR. BIRNKRANT: Well, it is also a dilemma for us, as well, to see snippets of data that look potentially promising, but given that it was submitted so late, it is difficult to review all of that data within such a short period of time.

Given that, as you answer the question for the treatment-experienced population, please let us know how important to the entire committee, the data from 045 would be in order to put wording in labeling pointing to use of this drug in the treatment-experienced population.

DR. GULICK: So, let's address that specific point from the committee. So, here is a study, we have seen the data, it has not been reviewed by the agency, and how important do we feel that that data is to include for the treatment-experienced population.

Dr. Fletcher.

DR. FLETCHER: Well, in my mind, it is the only data that really make the case from a clinical trial for using the drug in the treatment-experienced patient. If you have to look at just the 400, once daily, regimen versus Kaletra, it

wasn't as good as other available agents.

So, I think in terms of making the case for a role, the drug, safety, efficacy, and treatment-experienced, to me, 045 is essential.

DR. GULICK: Other thoughts on that?

Dr. Englund.

DR. ENGLUND: I agree. I think it is important, but I also can sense at least from the people I work with, and I know the FDA appreciates this, too, is the sense of urgency. We have patients that are running out of alternatives and it is of concern. We don't want to jump the gun too early, but we would have a problem to recommend it for naive and think that it's not going to be used in another way.

DR. GULICK: Other opinions about this? Dr. Mathews.

DR. MATHEWS: Let me say that I think we would not be well advised to take the extreme position of saying that because it's inferior to a Kaletra-containing regimen, it shouldn't be approved for treatment-experienced patients.

I think what should happen is that the data should be presented in the label to show that it did not perform as well as Kaletra, and the

precise clinical situation where it might be used is going to involve individualization of therapy.

I mean I have lots of patients who are having a lot of trouble taking Kaletra or other PI-based regimens that are very anxious to get to a simplified PI regimen. On the other hand, I am going to have to tell them, you know, you are barely controlled right now, and the small difference in efficacy between what you are on now and this more simplified regimen may cost you long-term virologic control, we don't know.

But I think those are the discussions that are going to have to take place in the office.

DR. GULICK: I would like to make a couple of points on this myself. We have been talking about experienced patients as if they were one group, and that is clearly not correct, and I think that that clouds our thinking when it comes to the optimal treatment of experienced patients.

043 was a study, yes, of experienced patients, but only 56 percent actually showed PI resistance upon entry into that study, and they were limited to have failed one protease inhibitor by history. So, that is what you would characterize really as an early failure group, and

I think the 045 study looks at a more advanced group with more PI experience.

Clearly, that is the biggest need in the clinic right now, is not so much the early failure people where you may have several options to choose from, but the later stages where you want some good options, and Chris' important point that this is of benefit in a salvage regimen. They are the same principles that apply in a naive regimen - low pill count once a day actually also apply in the salvage setting, as well.

The other point I wanted to make is that 043 really is not a study that we would do today because we would select, in a person who has failed one regimen, we would select the next regimen based on their resistance testing, which was not done in this study. It was done retrospectively to go back and look at where they were.

So, really, it is difficult to apply that study to the optimal treatment of the experienced patient today. Current guidelines, as was reviewed earlier by Rich D'Aquila and others say that you should do resistance testing in that setting. Pick the optimal regimen based on the results of resistance testing.

Again, not to criticize that study, it was probably designed before that was true, but it needs some interpretation in terms of how you would do it.

DR. BIRNKRANT: But if resistance testing were incorporated into the use of this drug, then, how would you feel using it then in a treatment-experienced population?

DR. GULICK: You are asking me directly or shall we ask the committee? I will answer. How about that?

I would say that based on the data that we have seen today, that in an experienced patient, you want to optimize their drug levels and that combining with low-dose ritonavir would be the way to go, analogous to all of the other approved protease inhibitors we have with the exception of nelfinavir. That is one man's opinion.

DR. KOWEY: First of all, I am a very naive person when it comes to all this, so take this with a grain of salt, but looking at this from the point of view of the safety side, and you emphasized that earlier, I haven't seen any data in the so-called experienced patients that make me believe that they are at any more risk than someone

who is relatively treatment naive.

So, having said that, and looking at the numbers, there are responders. There clearly are people who are responders even though the numbers are not as robust as you would like them to be. So, I guess I am having a somewhat difficult time understanding why you wouldn't want, as long as the data come in looking the way that you think that they should look, and after a thorough analysis, why wouldn't you want this combination available for people who haven't responded to other therapies as long as there is not extra safety concerns, which as I said, so far, looking at the data very superficially, we haven't really seen.

You have got gain, and you don't have too much of a wash, why not?

DR. BIRNKRANT: We have only reviewed 16 weeks of data. We haven't reviewed the 24-week data for safety yet. So, if we think that would be important. We don't want to rely on the 16-week data for use in this population just based on the 16 weeks. We want to see the 24-week data to make a decision.

DR. GULICK: Dr. Remmel and then Dr. Tephly.

DR. REMMEL: There is, of course, another class of experienced patients to consider, and those would be patients who already have disturbed lipid profiles and who you want to switch to lower their cholesterol or lower their triglycerides especially, and that may be in a slightly different class than what we are talking about in terms of failure. That clearly would be advantageous for many patients in addition to simplifying their regimen.

So, that might be a little bit of a separate category that one might consider.

DR. GULICK: Dr. Tephly.

DR. TEPHLY: Exactly. I was going to make exactly the same point, that we can't forget the advantage of the lipid-lowering quality of this particular agent.

DR. GULICK: Other comments on the experienced? Dr. Kumar.

DR. KUMAR: I want to echo some of the comments that Dr. Mathews had said. In the treatment-naive patient, I think it is an excellent drug, it's a drug that I feel very, very comfortable with, but in the treatment-experienced patient, using it by itself, with unboosted dose,

my concern is that failure begets failure, and in that setting, despite its convenience, the dosing, that it may lead to the development of more and more resistant mutants, so that is really what I am concerned about, using it as a single dose of 400 mg without boosting.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: Again, another question of the agency. It's this issue again about what if there was a recommendation for approval, what could go on the label in the pharmacology section. Could information on boosting be put into that section, or again, would the label really be constrained to information on the 400 mg dose?

DR. BIRNKRANT: There is a possibility that perhaps some PK data could be placed into the label in the appropriate sections.

DR. GULICK: Let's consider hyperbilirubinemia observed in the clinical trials so far. Comments on that? Dr. Tephly.

DR. TEPHLY: This particular drug is not the first one, I guess, to have demonstrated hyperbilirubinemia, so there is a precedent here already. I don't believe there has been a single case of hyperbilirubinemia reported in an adult

where there has been any toxicity due to this particular substance other than its cosmetic problem.

How far one goes down in age group is something that needs other comments, people who have had more experience in this, but I have had a number of experts, that in discussion on this subject, who have dealt with pediatric age groups, and other than the yellow color, the only problem seems to be the living life, and I am talking now about Crigler-Najjar patients who have values that are up in the extraordinary level, 100 mg/dl, and so forth.

Their only problem is that they want a liver transplant because they look yellow, and I don't believe that, unless someone has data from hyperbilirubinemia exclusive of hepatic disease, that there is any potential toxicity.

Now, in the very, very young, of course, there has been published some information on its deposition in the caudate nucleus and other extrapyramidal portions of the brain, and that is an area that I think needs to be discussed possibly in the future. There is no data on that now.

I know a little bit about UGT 1A1, and the

bilirubin is a specific substrate for this protein, however, we published a paper last year showing that there are two binding domains on this protein, and that bilirubin glucuronidation is not inhibited by a number of other agents which are also metabolized through the catalysis of this protein.

I believe that the steroid binding site is different than the bilirubin binding site, as well, and certainly different than the opioid binding site in this protein, so the drug-drug interaction may not be as important also as one might consider when one takes into account the substrate specificity of this protein.

To summarize, I do not see any problem of the bilirubin levels that are reported in any of the work that has been demonstrated here, and I would suggest that there probably won't be any problems in the future including drug-drug interactions with agents that attack the bilirubin binding site with several exceptions, and those have been reported in this work already.

DR. GULICK: Thanks.

Dr. Remmel.

DR. REMMEL: There are a couple of exceptions, and it may play importance in certainly

African populations and the Mediterranean area, and that has to do with cholelithiasis. There have been reports in terms of cholelithiasis in Gilbert's syndrome in beta-thalassemia, sickle cell anemia, and glucose-6-phosphate dehydrogenase deficiencies.

In fact, in sickle cell anemia patients, cholecystectomy is the number one cause of surgery in those patients. So, where you have a situation where you have a higher red blood cell turnover and a higher hemoglobin turnover, that is being metabolized down to bilirubin, theoretically, there could be a concern there.

Now, we do have a high African-American population who are taking these drugs, so that would be just a cautionary statement that those may be patients that we might want to watch for in terms of gallstone formation.

The other comment I had is there has been an interesting recent study that bilirubin is an excellent oxidant, in fact, it may be helpful for preventing ischemic heart disease, so that may be an additional benefit actually in a secondary mechanism.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: As a hepatologist who is frequently asked to evaluate patients with elevated bilirubins, as well as other problems, I also have a particular interest in this area. First, Gilbert's is not a disease, Gilbert's is a polymorphism that may, in fact, confer some benefit as was indicated in more than one area. There is evidence of anti-proliferative effects of unconjugated bilirubin.

So, what we see in terms of elevated bilirubin in this process is not the same as what we see in a cholestatic process. Someone mentioned early today a trimethoprim sulfa, which can cause a cholestatic process, but it's a conjugated hyperbilirubinemia.

The unconjugated hyperbilirubinemia seen here is not a disease, and that needs to be emphasized. However, the fact that patients have more cholecystectomies associated with hyperbilirubinemia is true, and it is due to a problem that exists in the community, that often patients who show up with some vague abdominal pain and an elevated bilirubin are not fractionated or fractionated or not recognized, and that leads those patients often to inappropriate surgery.

So, the problem here is one of education and recognition. The company has indicated that they have a plan in place to deal with this education, and that is going to be very important, but it is going to need to be emphasized in the label that this is a known side effect, again not a disease, of the use of this medication, and that just because a patient's bilirubin is elevated, doesn't mean that they have significant underlying liver disease.

Emphasis on the use of indirect bilirubin as a measure is important. There were some questions raised about the utility of screening patients for Gilbert's, and certainly the assays at least in research laboratories are available. I am not aware of a commercial test yet for Gilbert's. I wouldn't be surprised if some specialty labs are beginning to look at that.

However, most of these patients can be identified, the ones at greatest risk, simply by looking at their baseline bilirubin and looking again for the direct versus indirect fractionation, and you can make that determination before the patient ever starts the medication.

I do question whether this, in fact,

should be classified as a toxicity with dose reduction recommended at a certain level, because again, if you accept that this unconjugated hyperbilirubinemia is not a disease, then, there is little reason to do a dose reduction unless for the cosmetic reasons that a patient doesn't like the color of their skin and sclera, and if that is an issue, then, maybe this was not the best drug for them in the first place because you don't want to drop the dose and have problems with viral breakthrough because you are dropping the dose for the wrong reason.

DR. GULICK: Let's pursue that point for a minute. So, as I understand that the current proposal is not having dose reduction at all in the label, but recommending that Grade 4, which is greater than 5 times the upper limit of normal, bilirubin, would be considered to discontinue the agent. That is the proposal.

DR. MARCUS: That is correct.

DR. GULICK: Dr. Sherman, what do you think about that?

DR. SHERMAN: I think there is no reason to drop the dose based on that level if it is due to this drug. Again, a primary unconjugated

hyperbilirubinemia that is not in the setting of sepsis, where you could have hemolysis and DIC.

DR. GULICK: Is there any bilirubin where you would change your mind and recommend discontinuing the agent, if I pin you down for a level, that makes you uncomfortable to continue?

DR. SHERMAN: I would not stop the drug for that reason ever, but I don't think we are going to see levels in this disease--

DR. GULICK: Fifty, 60?

DR. SHERMAN: Well, you won't see that in this disease process.

DR. GULICK: Dr. Tephly.

DR. TEPHLY: I wholeheartedly agree. I don't think one should--this is not lead poisoning where you treat a blood level in children. I don't believe in treating a blood level. I don't think that is appropriate.

DR. GULICK: Dr. Fish.

DR. FISH: I think this will be patient-driven, and we have the indinavir experience. It was less frequent with indinavir, but we certainly learned to manage that, and we occasionally saw bilirubins go to 6 or 7. If the patient gets clinically jaundiced and they are terribly bothered

by it, they are going to want to come off the drug.

I think importantly, probably with indinavir, it was not of a frequency where we discussed that as a side effect when we started treatment. We talked about kidney stones and other things. But with this drug, I think it will be important for us, as clinicians, to discuss this with the patient, so that they are aware upfront that it could occur, in fact, maybe we could say it may well occur, and yetis clearly not harmful and be very reassuring upfront.

I think we will get a lot of people through that if they do go into these higher levels of hyperbilirubinemia, they may want to discontinue because of the cosmetic effect.

DR. GULICK: Shall we move on to the cardiac conduction part of the question? Let's actually start with the QT interval.

Comments about what we saw? Dr. Morganroth.

DR. MORGANROTH: I think the principal dataset that is important is the 076 trial, the so-called definitive trial. It is not perfectly definitive, doesn't have a positive control, has almost enough females to look at that issue. I

guess I am not too troubled by the dose, the super-therapeutic dose 800 because of the discussion that occurred. That is sort of a bit of a limitation, but nice to have of a wider range, but I am not sure because of the need to use normal volunteers and the bilirubin, and the ethics of all that, so it is not too unreasonable that the 400 and 800, and as was pointed out by the sponsor, the concentration differences even more than 2X, which, of course, is important.

The lack of a positive control, in my opinion, in this particular trial should be given little weight versus medium weight or more than that, because they had adequate numbers of ECGs, you know, over 10. Usually, 10 to 15 is the right number. They had a nice sample size, and they did adequate measurements in terms of manual, central lab, and they had a placebo, and they had it sounds like enough of a washout period that carry-over effects are probably not an issue.

The lack of any signal, meaning that the signal was negative by Fridericia's, which is, in my opinion, the only thing that counts, I would not think that Bazett's should be used at all, that the fact that there was both negatives compared to

placebo versus anything else make me very comfortable that the lack of the positive control is not critical, because I think the purpose of the positive control is to get these trials done with adequate sample size, with adequate number of measurements and adequate corrections and the like, and if not, you know, if there is something shorted by a good design in that regard, then, the positive control, of course, is the way to check that.

If someone wanted to use only 30 patients in a crossover instead of 72, or someone wanted to use 60 CGs instead of more, or what have you, so I wouldn't be too troubled by the positive control, because I know in the agency's analysis, that was an issue.

So, it is not perfect, but in my opinion, it is pretty close to being definitive, and without a signal on the QT, save for the 3A4 interaction issue, I think I would not be concerned at all about the QT.

DR. GULICK: Dr. Kowey.

DR. KOWEY: I will be a little less kind, I think, not that I think--this is obviously a very difficult problem area, and I do want to compliment the sponsor because I think that they have, to this

point, done a fairly good job of trying to understand two different issues.

By the way, QT interval, I have heard a lot of people talk about conduction abnormalities, QT is not a measurement of conduction, it is a measurement of repolarization. We do have a conduction problem, and that is the PR interval, and we have a repolarization issue, which is the QT interval.

I am not saying that just to be petty, but I think we need to be clear that there are two separate ECG issues that have to be dealt with.

As I said, I think that there has been an honest attempt to try to understand this, but there are many things about this particular dataset which I think are somewhat disturbing, and we need to make sure everybody understands.

Number one, I think that the preclinical studies are inadequate. I think stopping with a HERG assay and then one measurement of action potential duration in a Purkinje model, it used to be okay, and it is not okay anymore.

I think the guidance document that is now in draft had made it fairly clear that we need to do a better job of understanding these drugs

preclinically because it isn't just HERG. There are other mechanisms by which drugs may affect repolarization, and there are other models now that are highly available and not expensive, easy to do, that can give you more information.

So, when you get down to asking later about what kinds of things need to be done, I think I would like to see a better preclinical assessment of this compound.

The second thing is that it is a noncardiac drug that is going to be administered by noncardiologists, which means that it is unlikely that anybody is going to be paying much attention to ECGs.

We can pretend that somebody is going to get EKGs and look at them, but the fact of the matter is that when this drug is approved, it is going to be used by people who are not going to be looking at cardiograms.

So, that raises the bar somewhat, and to the extent that I would like to know as much as I can possibly know about the worst case scenario that you can possibly get with a compound like this, again, both in terms of the PR interval and the QT interval.

The third issue is that there is a metabolic inhibitor issue here. It is metabolized, and it is a common enzyme system, and we have spent a lot of time talking about this. Joel even brought it up in his talk about metabolic inhibitors and the importance. There is the opportunity here to have concomitant therapy which might grossly change the plasma concentration, in fact, we have seen that, that there are wide variations in plasma concentrations.

Now, there is a table on page 175 of the briefing document in which the sponsor has presented plasma concentrations which are way up at the upper end, they use the worst possible correction formula, which was Bazett's, and still didn't see anybody go over 500 milliseconds.

That is very, very reassuring, but it is in a retrospective kind of look at a dataset which is underrepresented by women who are typically the people that we worry about having QT interval issues, so I am also concerned about that.

The PR interval issue again is an issue because people who take these medications, when they develop diseases that may not necessarily be related to HIV, maybe exposed to drugs, which can

also have an effect on the PR interval, like calcium channel blockers, for example, and again, I think it is highly unlikely that people who are going to be prescribing this drug is going to be following electrocardiograms in people like that.

So, again, I would like to see more information of what happens to conduction, PR interval, as well as repolarization at the extremes of plasma concentrations, and I don't think that that has been as well explored.

Now, there is a good excuse for it. The excuse is that if you try to drive the plasma concentration too high, there is an issue with hyperbilirubinemia, but as I pointed out, I don't think that that would be an issue if you were to do studies in which the patients were not exposed or subjects were not exposed to that level of drug for too long a period of time, you might be able to gather more information about again the worst case scenario.

What these things many times come down to are not a question of approvability. This is under an approvability question, and I apologize because I don't think that anything that I have said necessarily goes to approvability.

I think that these questions more from the point of view of labeling than it is approvability, but in factoring in the benefit and the risk, I just don't--I feel differently than Joel, I think, a little bit, in that I am a little bit more, maybe a moderately more worried about this as an issue for patients, and I don't want to see it taken off the table. I think it is something that really has to be dealt with in labeling.

DR. GULICK: Let me just clarify one point. We are going to take a formal vote, so everyone will need to assess the risks and benefits, and come up with an answer for themselves, but in addition, our discussions are meant to help with the process of the labeling, so we are considering both here at the same time.

DR. KOWEY: Of course, I understand that. I really don't think again that this is an approvable--from my point of view--an approvable issue. These things that I just raised, I think that they are issues from two aspects. One is more study, and the second is proper labeling.

DR. GULICK: Mr. Sharp.

MR. SHARP: I want to bring up again the issue of combining drugs and what that means for

this effect that happens to people, both in the QT and the PR, concerned with--you said that all the protease inhibitors have an effect on QT promulgation.

After this drug is approved, doctors are going to give it to patients, and they are going to be taking all kinds of different combinations, so what does that mean in terms of these kind of--even though we don't really see the QT as an issue, that much of an issue here, what does that mean in the real world.

DR. KOWEY: Let me answer that. But I think that you just hit it right on the head, which is exactly what I was getting at. People are going to be exposed to many, many other kinds of drugs, and we have learned now our lesson that there are lots of drugs out there that not only affect repolarization, but can also affect conduction.

That is why I am saying that the two things that need to be done, that I don't think have been done yet, or a much better job of defining this problem preclinically, that is, understanding exactly what is going on in preclinical models, and, secondly, really trying to find the worst case scenario, that is, exposing

people to very high concentrations of this drug either by virtue of giving them high doses or using a metabolic inhibitor, and seeing what happens in the worst case to the QT interval, so that when this happens--and the PR interval--so that when this happens, we have some idea of what we can expect in the real world without anybody monitoring electrocardiograms because, let's face it, we may say we want that, but it is unlikely that it is really going to happen.

DR. GULICK: Dr. Morganroth and then Dr. Wood.

DR. MORGANROTH: I wouldn't want you to think that there is total consensus among cardiologists about this issue, so it requires me to make one point of disagreement with Dr. Kowey and point of agreement.

In terms of the PR interval, which we jumped to, I totally agree. I think that is an important labeling issue, I think it is a real effect. I think it puts some patients at risk particularly when they have calcium blockers on-board, as demonstrated by that case of junctional rhythm and death that was described earlier. So, I totally agree with that.

In terms of the other issue of whether or not it should be required to do sort of additional preclinical work on this drug relative solely to the QT issues, I have a disagreement because I think that I was very impressed that the HERG was not able to be 50 percent inhibited. The sponsor only showed it to get up to, if I recall, 30 percent or 32 percent or something, so it couldn't even push it to 50 percent.

Number two, I believe the sponsor did what I will call an almost definitive trial as described before, and I believe--and this is where we might disagree--I believe that the target species, man, trumps preclinical.

So, what we might find in preclinical would be very interesting from an academic point of view, but would not influence me personally at all about whether this drug needs more monitoring or more concern about its effect on cardiac repolarization.

I think the data we have, if you agree that the 076 is a near definitive or equivalent to a definitive trial, is negative, and it appears to be clearly that with no signal of the QT increasing, and as Peter pointed out, when you look

at the isolated examples even in women, even using Bazett's, with these high concentrations--now, there are not many because there is only a handful, half dozen or so, there was also a reduction in the QTc interval in those individual patients even by Bazett's or at least known change.

So, I don't think that preclinical data would--I don't have a question clinically that I need preclinical data to help me with, because I don't see any signal for the QT and I think a reasonably worked-up application.

Could they do another definitive trial, single dose, with a metabolic inhibitor or ignoring the bilirubin issue and saying who cares if you push a normal volunteer up to 5 or 10 level of bilirubin, you know, I think you would probably get that by an ethics committee someplace, because it isn't the toxicity, as pointed out, you know, and maybe get it by. Today it is very tough.

But I just don't see the need for that from the data we have to date, and it would make it from 90 percent definitive to 99 percent definitive perhaps.

DR. GULICK: Dr. Wood.

DR. WOOD: I would just like to echo the

issues that have been raised regarding concerns with labeling. I think even though the reality may be that clinicians might not be inclined to do EKGs, I think it would be very, very important, since the PR intervals has consistently been an effect that has been seen, so that practitioners are going to have to be made aware.

Specifically, there are a significant number of HIV-infected patients that have cardiomyopathy, that are on digoxin. There has not been any data presented regarding issues of prolongation of PR intervals in individuals who have an indication for a didge [ph] for cardiomyopathy, and I think it would be important, not only for didge, as well as other calcium channel blockers, but any class of cardiac drugs that may affect either conduction or repolarization in terms of some kind of warning and alert.

As it relates to the use of the 300/100 dosing in treatment-experienced patients, there is no data that was presented by the sponsor regarding PR interval issues in that dosing, and I would be interested in knowing about that because clearly, the concentrations were higher, which probably is responsible for the superior virologic efficacy

compared to the 400 daily, but I would also be concerned about the frequency of PR abnormalities with that dosing because we didn't see that data.

DR. GULICK: Does the sponsor want to respond to that?

DR. LAWRENCE: In my presentation, I lumped together treatment arms for the clinical studies, but we have that broken out by studies, so if you can present that.

[Slide.l]

So, if you look at the DASH 45 study, we did look specifically at a boosted regimen versus some comparators, and the incidence of first-degree AV block, 4 percent, is really right in line with the other treatment arms across a number of studies.

DR. GULICK: Could we get a couple more comments on the PR interval itself? Dr. Morganroth, just about the findings we saw today?

DR. MORGANROTH: I really don't have much to add than what Peter said earlier. I think the fact that in this development program, there has been no second and third degree blocks presented in the individual trials is somewhat comforting, but when one looks at specifically the couple cases

that were culled out where someone was on verapamil or someone was a very high-risk cardiac patient, I mean I think the labeling can handle that and manage that to make sure that treating physicians be very careful about the use of this agent with any drug that affects AV node, that may be an indication for an EKG if they want to combine the drugs to make sure that after one reaches steady-state or whatever, that someone is not sitting with a junctional rhythm because the AV node has been knocked out.

Again, most people would be symptomatic with that, with this kind of condition. They would complain of dizziness or their pulse would be very slow, et cetera, so I think that would be clinically, usually evident, but in the label, one should be alerting physicians about the interaction at the AV node. That is clear.

In terms of how important that is, you know, without seeing any second or third degree blocks, it is going to be an uncommon, you know, I wouldn't say rare, but it is going to be an uncommon phenomenon, and I think risk management should handle it.

DR. GULICK: Dr. Kowey.

DR. KOWEY: Well, there is always concern about how data that you see inside a very well done, well supervised clinical trial, how that applies to the universe of practitioners once the drugs are out and used, and you mentioned didge, cardiomyopathy patients also get exposed to beta blockers these days at a very high clip.

It is an interesting paradox because we are talking about heart block which predisposes the bradycardia, which is a very strong risk factor for the development of torsades for drugs that prolong the QT interval.

So, you could envision a scenario where a patient becomes very bradycardic and is exposed to a higher risk of developing torsades, which is the rhythm that Joel was concerned about, based on QT prolongation because of this very unusual combination of electrophysiological effects.

I am also kind of left with--it is an outside calcium channel blocker, and I guess that is the mechanism for the PR prolongation although we don't really talk about that very much. I mean the mechanism of PR prolongation here, we are assuming it's calcium effect, but as Joel pointed out, it does have a minor effect on sodium

currents, and in that one very, very severe case, not only did the person develop AV block, but they also developed bundle branch block, which is not what you expect from a calcium channel blocker, but you might see with a sodium channel blocker.

So, there is enough here that again I think it really does bear careful attention in terms of what you tell practitioners when the drug is available to them.

DR. GULICK: Dr. Kumar.

DR. KUMAR: I just have a question to both our cardiology consultants. Could you comment--and I had asked this earlier on--in clinical practice, if you use thiazide diuretics with this and patients become a little hypokalemic, what would happen to either the PR or the QT interval, and would that have a clinical relevance?

DR. KOWEY: Hypokalemia? Hypokalemia is a very important parameter for the QT prolonging effect because hypokalemia itself prolongs the QT interval, and we know is a risk factor for the development of torsades when patients are given drugs which prolong QT interval.

So, hypokalemia is something that we assiduously avoid in people who receive QT-prolonging drugs

for these reasons. So, it is important.

DR. MORGANROTH: In this case, if atazanavir does not affect the QT interval, then, hypokalemia and bradycardia prolong the QT just as Peter said, and has its own consequences from those primary conditions, but you wouldn't have to worry about any interaction if the drug doesn't prolong the QT.

If the drug does prolong the QT, which I don't find evidence for, as you know, at this point, that becomes important labeling information, which often says do not use this QT-prolonging drug in conditions such as heart failure, atrial fibrillation, all the points that I had made on one of my earlier slides of all the mitigating factors that can also affect the QT, and you get two QT prolonging at a time, you can get knocked over the hill with a bad arrhythmia.

But just the isolated factor itself of having heart disease or hypokalemia or bradycardia that is severe can, in fact, in some patients, cause torsade.

DR. GULICK: Let me just try to summarize what we have said, and then we are going to take a

formal vote on this. Regarding atazanavir for the naive population, there was a consensus that the drug is clearly active, that we saw convincing data compared to a tough comparator, which was an efavirenz-based regimen.

People noted the convenience in terms of pill burden once a day and a general impression that the side effect profile was reasonable in the naive patient population.

A couple of cautions where PK variability, and we had spoken some about food effects. In terms of the experienced population, that presented much more of a quandary to us and to the agency is what we heard.

We saw evidence of activity, but this drug less good virologically to the comparator arm, which was Kaletra based. The committee had a consensus that there was more concern about the activity of atazanavir alone in a treatment-experienced population.

We were interested to see the ritonavir-boosted data, but appreciate that this hasn't been adequately reviewed and that we don't have a lot of follow-up information there.

The suggestion by Dr. Fletcher that

perhaps PK information could be included in the label to help the clinician decide what to do was greeted with some enthusiasm, and then the point to make that resistance, as it should be used in the treatment-experienced population as consistent with general guidelines.

Other advantages of the drug in naive patients also apply to the experienced populations, and then the point made that when we talk about experience, we are usually talking about virologic failures, but Dr. Remmel made the point that another version of a treatment-experienced population are those who are doing well, but are having hyperlipidemia, and so using atazanavir in that population, we also saw some evidence that that would be a good use of the drug.

Some concerns in this group - drug-drug interactions because experienced patients often are on multiple concomitant drugs. Again, the feeling that atazanavir alone perhaps is not the optimal therapy or the optimal way to use the drug in this population.

Hyperbilirubinemia, people felt generally comfortable. We have a precedent with indinavir although it occurs less frequently. Several people

said this is not a toxicity, this is not a disease, it is really cosmetic, that education and recognition are probably the keys, and emphasis that this is indirect bilirubinemia, and that dose reduction was not supported by the committee on that basis.

Concerns about bilirubin, we heard a little about certain populations in pediatrics, gallstones were also raised.

In terms of the cardiac effects, QT interval, the 076 study felt not to be perfect, but pretty darned good, that there was not a signal using Fridericia method of the QT interval.

There was some disagreement about the need for further study in preclinical, and the point made that man is a pretty good model for men, and some disagreement about monitoring, whether routine EKGs or symptom-based would be appropriate, but no consensus.

The big caution here is using this drug with other inhibitors of the 3A4 enzyme system. In terms of PR interval, felt that this is a real effect and that some populations could be at risk particularly those with concomitant diseases or are on other medications including calcium channel

blockers. Again, some disagreement about the need for monitoring, the need for warning, and some reassurance that there was no secondary or third degree heart block.

With that, we are going to go ahead and take a formal vote, and the question that we are going to answer is do the efficacy and safety of atazanavir support its approval for the treatment of HIV infection, and the answer is yes or no.

Drs. Sun and Morganroth are not eligible to vote, so we will start with Dr. Kowey and go around the table. A yes vote is for approval, and a no vote is against approval.

DR. KOWEY: Yes.

DR. GULICK: Dr. Fish.

DR. FISH: Yes.

DR. GULICK: Dr. Washburn.

DR. WASHBURN: Yes.

DR. GULICK: Dr. Illingworth.

DR. ILLINGWORTH: Yes, I approve.

DR. GULICK: Dr. Remmel.

DR. REMMEL: Yes.

DR. GULICK: Dr. Tephly.

DR. TEPHLY: Yes.

DR. GULICK: Dr. Wood.

DR. WOOD: Yes.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: Yes.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: Yes.

DR. GULICK: Mr. Sharp.

MR. SHARP: Yes.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: Yes.

DR. GULICK: Dr. Englund.

DR. ENGLUND: Yes.

DR. GULICK: Dr. Kumar.

DR. KUMAR: Yes.

DR. GULICK: Dr. DeGruttola.

DR. DeGRUTTOLA: Yes.

DR. GULICK: And the Chair votes yes, making it unanimous, 15 votes for yes, and zero votes for no.

With that, let's take a 10-minute break.

[Break.]

DR. GULICK: Welcome back, everybody. We are going to go ahead and consider the next few questions.

Question No. 2. Does the safety profile of atazanavir warrant additional clinical or

laboratory monitoring? Some of the things that have been at least suggested in our previous discussion so far; liver function tests including bilirubin, EKGs, resistance testing. A suggestion was made about drug concentration or TTM for atazanavir, and then even Gilbert's gene testing has been raised in previous discussions.

So, we should focus on those and other thoughts about monitoring. Let's start with EKGs.

Dr. Morganroth.

DR. MORGANROTH: I personally don't see any indication for requiring an EKG to initiate therapy. I think that for the PR interval where this is an issue of even considering any type of EKGs, I think that it would be prudent to obtain an EKG in a patient who you want to use atazanavir with a drug that affects AV nodal conduction - calcium blockers, beta blockers, et cetera, or in a high-risk patient who is known to have AV nodal conduction disease - digoxin, you know, other manifestations have already been discussed at length.

So, there, I am not sure how that works in a label because there is lots of issues. I think the guidance should be that this interaction may

cause things and that one can sort them out with an electrocardiogram. I generally don't like to see that, sort of like required or implied to be required, because of all the complex reasons, problems that that causes.

DR. GULICK: Dr. Kowey.

DR. KOWEY: The PR interval issue I agree with. I am having a little bit of a difficult time with this because specifically, and we are going to probably continue to argue about this, Joel and I, but in the absence of what I consider to be adequate preclinical data, I am having a difficult time deciding whether I want to give this drug to somebody who has long QT syndrome, which is potentially what could happen if you said you don't have to get a baseline electrocardiogram to give this drug to somebody, you can just give it without knowing what the QT interval is.

The only population that I would be concerned about is somebody who happened to have the long QT syndrome and I didn't know it, and I gave this drug to them. Now, Joel is coming from the point of view, I think, without putting words in his mouth, that this drug doesn't really have an effect on the QT interval, and I am coming from the

point of view, well, gee, it comes from a family of drugs where we know that these drugs have an effect on HERG.

HERG is not the only mechanism by which these drugs can prolong the QT interval. There are other mechanisms for QT prolongation other than just the HERG. As I said, in the absence of really knowing enough about this drug's basic electrophysiology, the one population that I just can't answer is a long QT syndrome patient.

DR. GULICK: Can you tell us, what is long QT syndrome and how common is it?

DR. KOWEY: It is a genetic heritable disease. Patients have one of a variety of abnormalities usually of a potassium current, although there are some sodium currents which can also be affected, and the net effect is that these people have a delayed repolarization, which is reflected on the surface ECG as a long QT.

They are susceptible to development of that arrhythmia that Joel showed you on the slide, and that happening either spontaneously or under conditions in which their QT intervals is further prolonged either by an electrolyte abnormality, for example, or the concomitant use of a drug which

prolongs the QT interval unwittingly given to them.

Although it is not a very common disease, in fact, it's a relatively uncommon disease, there are families of these individuals. We discover more of them all the time. It is really kind of difficult to tell you exactly what the prevalence of it is, but it is not a common problem.

DR. GULICK: Can you give us a feeling for that? Just for the prevalence.

DR. MORGANROTH: Yes. The prevalence is about 1 in 5,000 for the gene mutation. There are people who don't know their part of the family or that have some subclinical disease, but it is not that different, frankly, if you have a patient who is on a long QT-producing drug. It seems to me it is not just long QT syndrome you are pointing out, it is that it is someone who is on some other drug that we know that causes a long QT, or develops hypokalemia, et cetera.

The question is under those circumstances, do you believe that this compound affects the QT, and if it does, then, you should be uncomfortable and want to have some kind of prohibition in the label to use it for all kinds of conditions as if it were a long QT, it seems to me.

So, I think I would argue that you have to drop back and say do you think this drug affects the QT or not, and if it does, then, you have got a whole labeling issue and monitoring issue. If it doesn't affect the QT in man, then, you don't have any of those issues, I would argue.

Therefore, you have to determine how you make that judgment, and it seems to me that if you did a preclinical additional testing, and let's say you found this drug affected IKS--

DR. KOWEY: It doesn't.

DR. MORGANROTH: Okay, that's right, they looked at that.

DR. KOWEY: Try something else.

DR. MORGANROTH: Whatever it is, it affects IK something, because there is a lot of IKs. So, it affects IK something and you learned that by doing preclinical testing, or it looked bad in a wet preparation or something. Then, I would argue hmm, boy, I would want to do a definitive trial in man to see if that is true in the target species.

So, that is where we disagree in terms of whether or not the human definitive trial trumps anything you see in preclinical, and no matter how

bad how the preclinical looks, if you do adequate studies in man, and there we can discuss how adequate the studies are in man including the 076 trial, but if you have done an excellent job there or good enough job there, then, you should be comfortable that it doesn't affect the QT, you don't have to raise the labeling issues about it, I would argue.

DR. KOWEY: There is two fundamental problems. One is that--maybe it's because I do some of this for a living, but I do believe that there are preclinical models that help you to understand the liability of the drug, and, number two, no, I don't think that 76 is the definitive study because the doses that were used are not custom--we customarily drive the doses higher.

Now, the exposures were fairly high for 800, but they still were not of the order that we usually see in trying to construct the worst case scenario especially when there is a metabolic inhibitor issue, and especially when the drug comes from a family where we know that those drugs have an effect on cardiac repolarization.

So, I don't look at 76 as being the definitive study that answers all the questions

that we need to answer, and therefore, I am not comfortable saying that there is no need for ECG monitoring of patients for QT prolongation.

DR. GULICK: Let me pin you down then. We have just voted to approve this drug, the label is going to be written. Do we require EKGs for every person routinely at baseline who starts this drug?

DR. KOWEY: Until I have more information about this drug to tell me that and to convince me that there is not a QT effect that I need to worry about clinically, the answer is yes.

DR. GULICK: Dr. Morganroth?

DR. MORGANROTH: I would say absolutely no. Of course, you have to expect that, right? But I would say absolutely no because there is a history in the agency of approving QT prolonging drugs without such a requirement.

Take moxifloxacin, which some of the people here in this room know more about than I do, I guess, or at least as much, about the QT issues, and that is a drug that affects clearly cardiac repolarization and HERG, is used in fairly sick people, you know, people with bad infections, it's a fluoroquinalone, and there is no requirement in Europe, Canada or U.S. for any baseline ECG

monitoring.

I am only specifically address the issue of do you need an EKG to start a drug that has a prolongation in the QT. Now, I would argue in this case, at best, we are not 100 percent certain. We would agree that we don't know 100.0 percent whether this drug affects the QT, and even if we are suspicious that it might, it can't be by enough or by a large magnitude because we would see some signals of that in man, in the study that was done.

So, therefore, I don't see why one would want an EKG at baseline, taking agency and practice into mind.

DR. KOWEY: The case of moxifloxacin, as well as ziprasadone, where again ECG monitoring was required, where datasets, in my opinion, were complete, that is, the drugs were worked up, there was definitive clinical information, about as definitive as you can possibly get, and I was much more comfortable with being able to answer the question that you are asking.

I guess it's a philosophical thing. If you don't know the answer to the question definitively, what do you do, do you assume you are okay, or do you assume you are not okay? I think that is what

you are hearing here, and my answer is you assume--I am sorry, I can't assume you are okay--and what Joel is saying, well, it can't be that bad, so you probably are okay, and that is the philosophy. It is more of a philosophical difference, I think, than it is a data-driven difference.

DR. GULICK: So, we have a difference of opinion from our cardiologist consultants. Anyone else on the committee want to ring in on the philosophical issue here?

Dr. Mathews.

DR. MATHEWS: I don't think this is a philosophical issue for me. I think whether it is or it isn't a direct effect on the QT interval, I think numerically, a much more common problem is going to be the metabolic inhibitor effect, which is real and uncontested.

Putting something in the label obviously is the first level of dealing with this, but in terms of educating physicians about these drug interactions, most of us do not read the labels. I think more and more people are using palm pilots or the internet to check for drug interactions, but as a person who was involved in a near fatal reaction with verapamil, a beta blocker, and another

protease inhibitor with asystole, I think guidance needs to be given on not something that says use caution, but exactly what is the recommended monitoring if you are going to put someone on combinations like that.

Could one or both of you address that situation in terms of what would be the recommended monitoring in terms of frequency, you know, when the electrocardiograms?

DR. MORGANROTH: I think there is no disagreement that for the PR interval issue, as Peter correctly said, we recommend that you absolutely consider the PR and the QT, two different separate issues.

For the PR issue, which is an AV nodal conduction, there is just no question, this drug affects it, it affects it predictably, it is dose related, and therefore, when you give it to a high-risk patient who has already got their PR interval in bad shape or potentially in bad shape, that you are going to want to look at the PR interval when you add this drug.

So, I don't think there is any controversy there. What you are hearing is the controversy is the other half, the other issue, which is the QT.

I think that the issue of whether you need an EKG to initiate drug therapy to make sure the patient doesn't start with a prolonged QT, is a matter of philosophy, I would guess. I mean it depends on how you interpret the data, and we interpret the data somewhat differently, and therefore, we come to different conclusions as to whether or not the EKG should be done because if you are not certain of the knowledge, Peter's argument, I guess, is we should to an EKG.

I am more comfortable with where we are with the knowledge, and even if there was some effect, I think tradition and history, as I said before, has not usually required a QT at baseline. So, I am not going to get an answer that is going to be a consensus of your two cardiologists that are sitting at the table.

DR. GULICK: Mr. Sharp, Dr. Fletcher, and then we need to move. Oh, sorry, Dr. Birnkrant.

DR. BIRNKRANT: If I could just interject at this point, given that we have two cardiology consultants sitting at the table with differing opinions, perhaps we could hear from Bristol-Myers Squibb's cardiologist, Dr. Ruskin, to hear his opinion on this issue.

DR. GULICK: Break the tie, you mean.

DR. BIRNKRANT: Exactly.

DR. RUSKIN: Jeremy Ruskin. I am a cardiac electrophysiologist at Massachusetts General Hospital.

I guess I will just try to make some very brief comments. I see no QT effect here at all. I don't see anything that would be gained by doing additional preclinical work because generally, additional preclinical work is done to address a small signal that is seen in the clinical development program, and to try to get a comfort level about relative safety particularly I think Dr. Kowey is referring to the wedge preparation, which looks at transmural dispersion of refractoriness. For me, that has no relevance in this particular development program because I see no clinical effect whatsoever.

The PR interval effect, I think is unequivocal, dose dependent, and not clinically significant when the drug is used by itself. The concern I have with this drug and all the drugs in this class is that they are 3A4 inhibitors, and drugs like verapamil, which are very potent negative chronotropes and negative inotropes, will

be amplified dramatically when they are used with protease inhibitors.

The cases that you have heard about are not due to AV block. They are due to sinus arrest with asystole or a junctional rhythm, and that is due to the effect of excessive exposures to calcium blockers either alone or in conjunction with a beta blocker in the setting of 3A4 inhibition.

So, for me, that is the major concern, and electrophysiologically, in terms of this drug alone, I have no concern about the QT effect because I think there is none, and with regard to PR, I think there is a numerically and statistically significant effect when the drug is used alone, but I think it is clinically insignificant except when combined with other drugs.

With regard to Dr. Kowey's concern about exposures, I would say that it is important to remember that this drug is a 3A4 inhibitor and a substrate, but when you use it in conjunction with ritonavir or other 3A4 inhibitors, the exposures that you get are significantly less than you get with 800 mg, and we have got the data on 800 mg that you have seen with regard to QT, and there is

no effect.

DR. GULICK: So, you would recommend not doing an EKG routinely at baseline?

DR. RUSKIN: I would absolutely not recommend baseline EKG screening. There are drugs in widespread clinical use with unequivocal QTc effects, measurable, defined, undeniable, that are used for much less serious situations than this, for which ECG screening is not recommended. I think it would have no role here except in the settings that have been described, that is, someone with known pre-existing heart disease, someone in whom you are considering the use of a concomitant calcium blocker or a beta blocker, all the things that as clinicians, we know to be associated with risk when you have a 3A4 inhibitor on-board. In those situations, there is no question that ECG should be done.

DR. GULICK: Thanks.

Mr. Sharp, then Dr. Fletcher.

MR. SHARP: That sounds like a labeling concern to me. What concerns me about requiring people to get an EKG before they take this drug is access, and will that bar them from getting access to the drug because they don't have access to an

EKG. I don't know how common, not often in every doctor's office, and sending them to a specialty is a problem.

DR. GULICK: Dr. Fletcher, then Dr. Kumar.

DR. FLETCHER: My comment really goes back to a point that Dr. Mathews made about drug-drug interactions, and I guess specifically then to the 045 data and whether any information on the boosted dose of atazanavir can be put in the label.

Obviously, the 045 data are out there and it seems to me that if atazanavir is finally approved by the agency, that clinicians in some cases will use atazanavir with ritonavir. So, it seems to me we can't ignore that, and therefore need to find some way--and I think the agency and the sponsor certainly must have some ability to work out something acceptable--where at least pharmacokinetically, those type of data are there, I think because they directly go to this risk issue we are talking about here with now atazanavir being used with one of the most potent CYP inhibitors that we have.

So, while I think the issue bears on the 045 and data in treating HIV treatment-experienced patients, I think it really also comes in, in this

risk issue with drug-drug interactions.

DR. GULICK: Dr. Kumar.

DR. KUMAR: My concern comes to the fact that data--that swayed me into saying that with the 300, 100 milligram dose. But that is not the dose that we approved, but that would be the dose that is most commonly going to be used in treatment-experienced patients, but we have no safety data on that.

The only safety data that I can see is on the bilirubin level, that we have all agreed is not a toxicity data, but there is nothing on what happens to the PR interval, the QT interval, or any of the other safety information with that dose, but just the dose that is going to be used in treatment-experienced patients.

So, I think not to be upfront in getting more safety information until we are sure that there is no safety concerns, I think is a big mistake. I don't know what exactly, how many EKGs, when the EKGs, that is beyond my area of expertise, but I think without that safety information, all we saw was some tantalizing information of the effectiveness, but nothing on safety.

DR. GULICK: I thought we did see some--I

see lots of shaking heads over there--didn't you show us a slide with the--could you show us that slide again? If you could walk us through this again, that would be helpful.

[Slide.]

DR. LAWRENCE: This is a breakdown by study of the PR interval data focusing on incidence of first-degree AV block. So, in the DASH 45 study, we do have electrocardiograms on study and incidents of first-degree AV block for the boosted regimen is 4 percent, so this contrasts within the study with 6 percent in the atazanavir/saquinavir arm, and 4 percent in the Kaletra arm.

If you march across the other studies, it is right in line, if not, a little bit less than the experience in some of the other studies.

DR. SCHNITTMAN: Let's show the core safety slide on 045, as well.

[Slide.]

As presented earlier, here is the Grade 2-4 related AEs through 24 weeks, so again this is not reviewed by the agency, this is our updated data here showing those that had greater than 5 percent of subjects with these AEs.

Essentially, the incidence of jaundice in

the boosted setting is slightly higher than what we saw in unboosted, but not substantially higher, and otherwise, the safety profiles are quite remarkably similar to the unboosted setting.

DR. GULICK: So, just to say again, we are in a bit of an awkward situation to have some preliminary data that hasn't been well reviewed by the agency, let's face it.

DR. LAWRENCE: I could also show QT data from the DASH 45 study.

DR. GULICK: Sure.

[Slide.]

DR. LAWRENCE: So this will be the same layout as the PR data I just showed you, looking for outlier values by gender. Normally, we would have a greater than 500 row, but those were zeros across the board, so a very low frequency of subjects with values just outside of the normal range defined by gender. Again, here is 45.

DR. GULICK: These are 16-week follow-up or 24-week follow-up?

DR. LAWRENCE: These electrocardiograms represent, in the different studies, there was a different frequency of collection, but, for example, in 43, we collected electrocardiograms

baseline, Week 2, Week 12, Week 24. In 45, we collected at baseline and Week 4, so they do reflect some chronic dosing.

DR. KUMAR: For the 045 data, is that safety data the end of 16 weeks, 24 weeks, what time period did you show us?

DR. SCHNITTMAN: That particular slide was the 16-week safety update. Now, that was actually in the hands of the agency.

DR. GULICK: So, that was 24-week that he showed before.

DR. KUMAR: And this one?

DR. SCHNITTMAN: This one was cut at pretty much at the time of the safety update, but as I said, patients were getting it at zero, Week 2 or 4 and Week 12, so they would have had two or three sets of three EKGs probably by the time they entered this dataset.

DR. GULICK: Okay. We are going to need to keep moving here, so again, going back to the question of EKG monitoring, difference of opinion on routine EKG monitoring, more concern in patients with pre-existing heart disease or going on concomitant meds, such as calcium channel blockers.

Then, the point made again that a

ritonavir-boosted regimen could provide some more concern for using--or concern in terms of levels.

We are supposed to consider other parts of monitoring. Let's go to liver function test monitoring.

Dr. Sherman.

DR. SHERMAN: We already had considerable discussion about the bilirubin and I don't think we need to reopen that at this point. The question is other liver function tests monitoring, and I am not quite as sanguine about that. I am concerned about patients on these medications being followed for evidence of liver toxicity, and I think there should be a regular monitoring schedule for liver enzymes recommended.

I don't know what that is going to be, certainly an early timepoint sometime between 4 and 12 weeks would certainly be reasonable after a baseline value is obtained to look for changes.

However, data from the ACTG and other sites suggest that toxicity associated with PIs as a class can occur almost at anytime out in the course of following patients, maybe between the six month and a year mark just as common as before. So, repetitive monitoring with liver enzymes is

probably indicated.

That is the big issue in terms of basic monitoring. I will have some comments later in terms of perhaps future studies that may be needed to raise the bar with some of these issues, but I don't think they are applicable here.

DR. GULICK: Other comments on routine LFT monitoring besides what was said? Dr. Fish.

DR. FISH: The chemistry panels that we typically order just have the total bilirubin on them. These are designed based on kind of the Medicare guidelines as what they will cover, and so on, so just that caveat of requesting the indirect at least once probably when a patient has hyperbilirubinemia to prove that it is indirect.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: That's interesting because I think that is an issue and there is another monitoring issue related to bilirubin, and that is that a change that occurs, suppose a patient starts the drug and their bilirubin goes to 1.9, 2.2, which would be a fairly common range for a patient particularly with a heterozygote, Gilbert's.

I think that one of the issues is how do you not miss, not drug toxicity, but the evolution

of another hepatic process, and if we are going to get liver profiles over time, then, a later change in bilirubin certainly should be noted as something that requires further evaluation of etiology and that she should not just assume then from that point on that, well, this patient is on this drug, and bilirubins are up, and we never have to worry about it.

DR. GULICK: Other comments?

Okay. Resistance testing. I guess our consensus before was that we should follow standard guidelines and a that treatment-experienced patient should have resistance testing prior to starting the regimen. That is not different than current guidelines.

Gilbert's genetic testing. Dr. Sherman, you mentioned before is not really routinely available.

DR. SHERMAN: It is not routinely available and as I indicated, I did not feel it is routinely indicated because you can look at a much cheaper assay to determine if Gilbert's is present.

DR. GULICK: Then, Dr. Remmel, you suggested maybe TDM would be an interesting thing to think about for this drug.

DR. REMMEL: Certainly, the sponsor has shown, at least in a naive patient population, that we have good effect with this drug, however, I think this would be helpful. I mean I personally believe that we can learn something from doing this. We have other drug classes where we do it routinely, epilepsy is certainly an area that I have been involved with a long time, and we do that routinely.

It is not something sponsors like to hear, but I think that we can understand more about this drug. It does have a very large variability in the PKs when it is not taken with a boosted ritonavir dose, and I think getting an idea of at least a trough concentration given the cost of these drugs and if there is a demand, there will be availability to do the levels. There is already a company set up to do that, so it is really not overly burdensome.

Now, it may be overly burdensome for certain patients and certain types of practices, but I think from the company's standpoint, I would want to know where is my trough levels. It might help me to better design a Phase IV trial. It certainly would be useful in a situation when we

have experienced patients and we are talking about failure, that should be just as important as genotyping and phenotyping.

DR. GULICK: Dr. Fletcher, anything to add?

DR. FLETCHER: I would agree. I think as a Phase IV study, this would really be a worthwhile study to consider. It actually goes to Dr. Sun's question about what was the incidence of pharmacokinetic reasons for failure in patients, and if you look at the well-controlled pharmacokinetic studies that the sponsor presented, the range of trough concentration goes down to 12 nanograms per ml, which is below the adjusted IC50 and I think has to clearly put a patient at risk of failure.

So, if there is a strategy by which not only in the experienced patient that Dr. Remmel talked about, but in the naive patient where the best response is always to the first regimen. If there is an opportunity to improve the rates of response in naive patients, I would think that would be good for patients, good for the sponsor to take a look at. So, I would encourage some serious look at whether therapeutic drug monitoring could

improve response of patients to this drug.

DR. GULICK: Any other routine clinical or laboratory monitoring that we want to suggest or talk about?

Dr. Remmel. I don't mean for future study, but for the label now.

DR. REMMEL: I am not sure where this fits, but in terms of drug interaction profiling.

DR. GULICK: Let's come back to that one. That is an important point, but let's come back.

Dr. Englund.

DR. ENGLUND: I think the one thing the sponsor has shown is the effect if someone is positive hepatitis B, hepatitis C, which, in fact, should be routine care for patients anyway, but I think in this particular case, the physicians taking care of patients should know the patient's hepatitis status, not that you would necessarily stop it, as we said, but that would help to explain after you initiated therapy.

DR. GULICK: Good point.

So, consensus sounds like routine monitoring of transaminases to fractionate bilirubin if it's elevated as per clinical practice, to check baseline hepatitis serologies,

and again a disagreement on EKGs in the routine setting, but indicated in other settings.

Resistance testing is clinically indicated and none of the other tests routinely is the consensus of the committee.

Let's move to Question 3 because Dr. Illingworth has to leave in a couple minutes anyway.

Does the effect of atazanavir on lipid parameters offer patients a clinically significant advantage over other treatment options? Dr. Illingworth, let's start with you.

DR. ILLINGWORTH: Yes, I think it does. I think the rise of about 15 percent in LDL and the rise in triglycerides on other protease inhibitors, and the lack of effect of this drug are very positive benefits. Obviously, the long-term therapy is important.

You are going to also, by using this, you are going to have less patients who are on statins or other drugs that may interact with other drugs. So, atorvastatin, simvastatin, those are metabolized by the cytochrome p450/3A4 system, so not being on those may have benefit.

So, monitor the lipid profile, but

obviously, if a drug does not have any adverse effects on plasma lipids, that's positive.

DR. GULICK: Could you comment on the fact that we didn't see effects on lipodystrophy or cardiovascular events?

DR. ILLINGWORTH: Probably the time frame to show an effect on cardiovascular events in patients without known cardiovascular disease or without particularly high levels of LDL, you are going to take five years to show a benefit in prime intervention.

In second intervention, patients with known vascular disease, then, obviously, the second intervention trials are shown in about the first two years even in patients where the LDL is down about 100. So, if you have somebody with known vascular disease, getting the LDL down lower has benefit, that is clear.

There have been five big trials with simvastatin, pravastatin, lovastatin, and in the recent publication last year, the Heart Protection from Rory Collins at Oxford showed a benefit even in patients with LDLs of 100 that are starting out with vascular disease, getting it lower.

Beyond the NCP3 panel, one of the debates

we had was, ,well, should we have the optimal LDL equal to or less than 100, which was on the NCP2 panel, or less than 100. The vote was less than 100. The clinical trial data gets more and more beneficial, that lower is better.

So, using a drug for HIV, that does not adversely affect lipid profiles, I think is very positive events.

DR. GULICK: Again, could you comment on the lipodystrophy? We heard that there was not a lot of difference in the self-reported lipodystrophy. Is it a timing issue again?

DR. ILLINGWORTH: It may well be, yes. We don't really know what causes lipodystrophy in all these patients anyway.

DR. GULICK: Other comments? Dr. Kowey.

DR. KOWEY: I guess I am a little hung up on the term "clinically significant." First of all, I agree that if you had your druthers, you would love to see a drug like this not raise LDL levels and not raise cholesterol levels, there is no question, but there is a statement in here that says "clinically significant advantage." Unfortunately, because of what you said, and I agree completely, there is not enough time in these

trials to really see the effects. The age groups are wrong, these people don't have a cardiovascular disease going in. There is really no reason to think that you would have seen a difference. I mean it would have been impossible to see a difference in cardiovascular endpoints.

So, again, it is very analogous. The question is in the absence of definitive information, what do you say. I think it is reasonable to say it is better to have a low cholesterol than a high cholesterol, it is better to have a low LDL than a high LDL, but this says "clinically significant advantage," and I don't know has that really been proven for this dataset. I guess it's a question.

DR. GULICK: Dr. Illingworth, a response?

DR. ILLINGWORTH: One of the issues I put in, and I know I was going to give you, for Phase IV studies, were we to look at markers of vascular information, so look at perhaps the effects of different protease inhibitors in different treatments for HIV on things like high sensitivity C-reactive protein is a marker for vascular information, HSCRP.

DR. GULICK: Mr. Sharp.

MR. SHARP: I guess something that concerns me is once the drug is approved and marketed, how the company is going to advertise for the drug. Do they tell everyone that it is good for--that it improves lipodystrophy? People in the community and patients especially don't really know the difference between elevated lipid levels and body shape changes, and they consider them all one thing, so I would just urge that once a drug is approved, that it is marketed towards saying that is has a less effect on lipid levels than lipodystrophy.

DR. GULICK: Maybe we could ask Dr. Grunfeld to comment on this.

DR. GRUNFELD: Carl Grunfeld, Professor of Medicine, University of California at San Francisco.

I agree with Dr. Illingworth that we don't know the cause of lipodystrophy. In fact, there is a debate as to what the syndrome or syndromes are, and I think you can look at it as two components, lipoatrophy and lipohypertrophy. There are associations of lipid abnormalities or glucose abnormalities with the fat changes, but I believe there is no credible evidence linking any of the

metabolic changes as causal towards the fat changes.

Mr. Sharp is correct that not everyone in the community or among investigators understand it. So, for other drugs, there is not an inherent link between any particular metabolic change and any particular change in fat distribution causally in that direction metabolism to fat distribution. There is no reason to expect, at this early point, in trials there to be a change here.

The fat changes reported in the early dexa data show an increase in fat consistent with return to health, and no sign of the lipoatrophy, which is the most stigmatizing version, but again, it is only 48-week data at which point you would only expect to see return to health, and not the onset of lipoatrophy.

The causal link between any of the drugs in the class is of great debate among the researchers in the field.

DR. GULICK: As long as we have you there, let me pose this question directly to you. Does atazanavir, its effects on lipids, offer a clinically significant advantage over other treatment options?

DR. GRUNFELD: Well, I think we may need some comments from Dr. Pearson, but I would actually like slide 69 up. I agree with Dr. Illingworth that any change, particularly now that we know that people are at high risk and Dr. Pearson will address that, would be better, and I think Dr. Pearson would be better to address the risk.

[Slide.]

But this is an example of the use of lipid-lowering agents in trials, and I want to point out that particularly in the experienced patients where we have a bigger effect, the amount of lipid lowering agents in the comparator was much higher than in atazanavir in 043, and in the comparator of lopinavir/ritonavir in 045 versus atazanavir/ritonavir in 045.

The actual use is lower, indicating that among other things, this is a major concern among practicing physicians, that people are being aggressively treated because the risk factors are high in HIV population indicating the need for aggressive treatment, and there is less need for treatment with less complications.

I think the terms of risk profile would be

better addressed by Dr. Pearson.

DR. GULICK: Okay.

DR. PEARSON: I am Tom Pearson, Professor and Chair, Community and Preventive Medicine, University of Rochester. I also direct the Preventive Cardiology Clinic where we have been seeing increasing numbers of patients with HIV positivity and with lipid abnormality, and I think have been looking for options for them.

I think in trying to rationalize what Dr. Kowey and Dr. Illingworth said was I agree with Dr. Illingworth that these lipid changes of 15 to 20 percent for LDL and 20-plus percent for triglycerides are those that we oftentimes try to attain with lipid medications lowering them, so this is somewhat the flip side.

But I also agree with Dr. Kowey that this is a young group. The recent Fozetti [ph] study in The New England Journal, only 11 percent of those individuals were above the age of 55, 2 percent apparently, nationally, are above the age of 55.

This is an epidemic in progress, in happening, not here yet. So, I would like slide 6A5, talking about the risk of this group because in my experience, clinically, this is a group with

a lot of risk factors that really haven't happened yet.

[Slide.]

You can see here. This is from the DAD study, 23,000 HIV-positive patients. You can see that high level of smoking. These are risk factors that occurred probably even before HIV positivity.

You have some others. Dr. Grunfeld, for example, is an author of some of the first studies showing that elevated triglycerides are, in fact, characteristics of HIV-positive patients, and then you have some risk factors that are probably due to therapies, such as protease inhibitors.

So, if I could then relate these as important 6U5. What we know from the Framingham heart study is that in the presence of other risk factors, that increase in cholesterol from low to high has a much greater absolute change.

On the bottom, you see various combinations as you go from left to right, to more and more risk factors. Again, we are showing a multiple risk factor profile in the HIV-positive patient currently.

You can see as you go from 185 to 335 in cholesterol, you see this, as you get more and more

risk factors, these large absolute changes. So, if we were in the right age group, here, these individuals being in their mid-50s, we would be seeing this in the HIV population.

I think this is what we want to avoid, and we want to come up with options that I can give in my preventive cardiology clinic to the HIV-positive patients in sending a letter back to the referring physician about some other options for them.

DR. GULICK: Thank you.

Other committee members who would like to ring in on this issue? Dr. Englund.

DR. ENGLUND: As a pediatrician, I would like to say that we have very grave concern about having high cholesterol levels in our very young kids when we expect them to live for 20 and 30 more years. Unfortunately, you don't have quite enough data for us, so I can't say it, but I would say that in the future, that is what we can look forward to.

We are very concerned with having even moderately high levels, and I think our pediatric colleagues can speak to that, in some of our kids.

DR. GULICK: Dr. Kumar.

DR, KUMAR: I do agree that there is a

very favorable lipid profile, but I do want to add and the sponsor themselves had said that any information on lipodystrophy was only passively collected, there was no concrete attempt to collect this data.

So, all we can say is that it has a favorable lipid profile.

DR. GULICK: I wanted to raise an issue where I heard something different from the sponsor and the agency, and it was about the study of people on nelfinavir who switched to atazanavir, and the sponsor said that there was a return to baseline levels of lipids and triglycerides, the agency said that it wasn't really baseline, or maybe I misunderstood, but could we get some comments on that, did I mishear that?

DR. MARCUS: I don't think we have any major disagreement on this point.

DR. GULICK: So, you would agree that they went to baseline?

DR. MARCUS: Yes. I actually put up a slide looking at triglycerides over time for studies 007 and 008, and not the switch study.

DR. GULICK: Thanks for that clarification.

Dr. Mathews.

DR. MATHEWS: I just want to make a point regarding what is known or not known about when the drug is combined with ritonavir or other protease inhibitors, because, you know, until a study is done comparing the boosted to the unboosted regimen, at least when I asked this morning, the sponsor didn't have any specific comments about how much of the effect might be attenuated.

So, in the treatment-experienced patient where there will be a tendency to use it in that way, I think the label should not overstate the benefit in terms of lipids until there is data on that point.

DR. GULICK: Could the sponsor, do you have data from 045?

DR. GIORDANO: Yes. Again, the data that I have, 045, are comparative data, atazanavir with ritonavir versus lopinavir with ritonavir, so I would like to show the 045 LDL cholesterol data, so 6G8.

[Slide.]

Again, with regard to LDL cholesterol, you see large differences in the LDL cholesterol values at the end of 16 weeks of therapy with atazanavir

with ritonavir, which is in green, or lopinavir/ritonavir as a comparator, which is in orange.

Similar effects are seen if I showed you total cholesterol. What I will show you now are fasting triglycerides, so 6J8.

[Slide.]

Again, in green, and in blue are the two atazanavir arms. The green reflects atazanavir boosted with ritonavir. Through 16 weeks, there is very little change in the fasting triglycerides, whereas, the comparator agent lopinavir/ritonavir is associated with a 34 percent increase in triglycerides.

So, the patient who is facing the choice at the time of needing a treatment regimen when they are heavily treatment-experienced, would have significantly lower lipids if treated with ritonavir/atazanavir as opposed to lopinavir/ritonavir.

DR. MATHEWS: Yes, but that isn't the question that I was asking. It was the effect of boosted atazanavir compared to unboosted. In one of the slides that Dr. Grunfeld showed, when you looked as an indicator, the proportion on lipid-lowering

therapy in experienced patients from unboosted, it was like 4 percent boosted, it was 7 percent, which is nearly twice as much.

So, I think it is relevant to know what the direct comparison is, how much of the benefit is lost if it's boosted.

DR. GIORDANO: We don't have data which is a head-to-head comparison of atazanavir boosted versus unboosted, so I can't answer that specific question, sorry.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: Actually, before you leave, the same subject. Do you have the data broken out about patients that were not on any lipid-lowering agent and the comparison between the arms?

DR. GIORDANO: The data that I have shown you reflect data through institution of a lipid-lowering drug. We also did sensitivity analysis to look at what happens to the effect when you added those values should lipid-lowering therapy be added.

Interestingly, the only time it makes any significant differences on the experienced patient studies, because far greater numbers of lopinavir/ritonavir subjects instituted therapy for

high lipids, so that brought down the means for the lopinavir/ritonavir arm because they were censored.

So, independent of the analysis done either if you include lipid-lowering agents in or not, the same statistical differences are observed, and the same large differences are observed.

DR. GULICK: Let me bring us to a close on this question.

The question, atazanavir's effects on lipid parameters offer a clinically significant advantage over other treatment options, the consensus of the committee is yes, that there are clinical benefits. The immediate ones are reducing the number of anti-hyperlipidemic agents that are needed, so this improves convenience.

As was stated by Dr. Illingworth, reductions in cholesterol LDL and triglycerides on other studies we know provide benefits. It is probably too early to tell, as several people mentioned, whether these will have repercussions on cardiovascular events here.

The HIV-infected population is younger than other populations that have been studied, but may have more other risk factors, such as smoking, and as Dr. Englund pointed out, the pediatric

population presents an interesting group because we are going to be treating patients for years with some of these agents.

There was a sense that we need more information on lipodystrophy, and we heard that there is really a disconnect. We don't know the mechanism of lipodystrophy, there may be a disconnect between hyperlipidemia and lipodystrophy.

Finally, concerns about using boosted atazanavir with ritonavir on lipid levels, and we saw some early data from the sponsor.

Let's move to Question 4. Based on resistance data, what recommendations would you have regarding the use of atazanavir in naive and experienced patients?

A thought-provoking question clearly. Let's start off with the naive group. So, we have heard a story about atazanavir, that it has a signature mutation which is unique, which retains sensitivity or perhaps provokes hypersensitivity to other protease inhibitors.

Does that impact on your choice of agents for naive patients in general? Is that a good thing?

Dr. Fish.

DR. FISH: As a sequencer, this is going to be a great drug, so for naive patients, the comment was made in terms of regarding doing resistance testing very early on. Someone mentioned the revision of the guidelines for use of resistance testing.

If we go there, then, that would help us even further in ferreting out those few naive patients who might get some mutation that was transmitted, some PA mutation where atazanavir might have decreased susceptibility, but otherwise, it looks very good in the naive patient population, and we have good options afterward for when a patient might fail if they are failing that component of their cocktail.

DR. GULICK: Can I make a comment myself, that a lot of what we heard in the presentations today were about the initial segmentary mutation that you see with atazanavir, and actually the statement was made more than a few times that resistance uncommonly develops to atazanavir.

But I guess what I would point out is in the studies, when people broke through, when they had virologic failure, they were quickly attended

to, resistance testing was sent, and this was acted on quite quickly.

In clinical practice, that is often not what happens, people continue regimens in the presence of ongoing viral replication for longer periods of time, and I don't know if we have data to show for this, but with other protease inhibitors, that leads to an accumulation of mutations and eventual cross-resistance to the class.

DR. COLLONO: Rich Collono again, BMS.

Let me just show you two context slides and then I will show you a specific slide to that answer, because there wasn't much really discussed about the I50L, and we need to understand where the I50L is.

Could I have B1, please.

[Slide.]

Again, the resistance profile is quite distinct and we have a very unique signature mutation. I just want you to understand why the signature mutation actually comes up. In treatment-naive patients, 100 percent of the time we find 23 isolates give rise to the I50L.

In treatment-experienced, if you use

atazanavir and saquinavir, one never sees the I50L. Instead, you go down a bunch of normal pathways that you would see with other PIs.

When you treat with atazanavir or boosted atazanavir, the experienced population, we have nine isolates, about 20 percent, that actually do give the I50L mutation, so it is not just naive, it is also those treatment-experienced patients that are susceptible to atazanavir at baseline.

If I can have the next slide, B2, please.

[Slide.]

The consequence of having the I50L mutation is shown here. Taking all those isolates that I showed you on the previous slide and simply dividing it into three groups, those that came up with the I50L, which are shown in green, you get specific resistance as mean change from baseline, just to orient you on the slide.

You get a mean change of 10-fold to atazanavir, so atazanavir's specific resistance which people have referred to, but as you can see, you get an increase of susceptibility to each of the other PIs across the board, and this is pretty universal whether it is from naive patients or from experienced patients.

In contrast, if you get atazanavir resistance through a different pathway, it does not involve the I50L, then, you clearly see what you have here in the blue bars where you get resistance to atazanavir, but you also get increased resistance to the other PIs.

The third one is just saquinavir/atazanavir, which is not important other than to say that clearly you get resistance to atazanavir and saquinavir, again increasing the resistance level to all of the PIs.

Now, as to your question, what happens after that, if I can have B-14, please.

[Slide.]

Once that I50L mutation is there, we have, unfortunately, only two isolates, but perhaps it starts to answer the question. We have very few, as you can see, I50L isolates to deal with, but we have two, one that continued on for 12 weeks, one that, more importantly, continued on for 24 weeks.

Here is the profile again where you have resistance to atazanavir, you have increased susceptibility by the numbers being 0.4, 0.3, et cetera, to the other PIs, and I have viral load here. As you can see, there was really no change

in viral load over the 12 weeks.

More importantly, for the one that was for an additional 24 weeks, we see no real change in increased resistance to atazanavir. We maintain this phenotype associated with the I50L, that is, increased susceptibility to the other PIs. Again, viral load is very steady and stable.

If you look at the genotype of those two sets of isolates, in the first set, you see no additional mutations being put in, despite continuing on atazanavir.

In the second set, we see a couple mutations bouncing around, 16 disappears, comes back. We don't think it is really relevant. 33F comes up, 64V comes up on top of this background, but again, there is no real impact on the phenotype. So, this is the data we have now, very limited, but to answer your question, this is the data that we have.

DR. GULICK: So, 100 percent of these two patients did not have any evolution. As a virologist, Rich, would you like to predict what will happen as people continue to stay on this longer term?

DR. COLLONO: Of course, they are going to

evolve to additional ones, but it is not--I guess the key point with the 50L, it is not a quick stepping stone where you get 50L and immediately go on to the next version. We have no indication of that in vitro or clearly in a couple clinical patients that we have.

DR. GULICK: Let me ask you two follow-up questions. When you call someone "treatment experienced," that is on the basis of history or those people have evidence of protease inhibitor mutations in the slide that you showed?

DR. COLLONO: The treatment experienced were basically entry into the program, qualified for the entry into those experienced programs. It doesn't necessarily mean that they were resistant to multiple PIs.

DR. GULICK: So, that is my question. If someone has PI resistance mutations, goes on atazanavir, have you ever seen, in that scenario, that they only come through with an I50L as their next mutation?

DR. COLLONO: Yes. Of those nine isolates that developed the I50L, all of those developed an I50L on top of an atazanavir resistance background, or in one case, we have one in the boosted from

045, actually, that was resistant to four PIs on baseline, but the I50L also. So, yes, it does happen, it is not just in a background of no resistance.

DR. GULICK: Great. My second specific question is do we have any clinical data from someone who was naive, went on atazanavir, failed with the I50L, and then went on to another protease inhibitor-containing regimen, is there any clinical data?

DR. COLLONO: There is no clinical data.

DR. GULICK: Dr. Sun.

DR. SUN: I have sort of a similar question, which is did any of these patients, when you detected the I50L, and thought maybe it was due to adherence or compliance issues, go back on atazanavir.

Sort of the corollary would be, if the answer is no, is it your interpretation of the data that the I50L is sufficient to confer clinical resistance to atazanavir by itself, so analogous to the 184V for 3TC or the NNRTI mutations?

DR. COLLONO: The I50L, by itself, when you put it into recombinant clones as a single mutation, will give you a decrease in

susceptibility, but the I50L alone does not give you a resistance level high enough to overcome the PK multiple that we have.

So, the I50L is always in a background of 10, 12, 14 other mutations. We have no clinical isolates that only developed the I50L. There are just, of course, other mutations there. There is just no pattern to those mutations that are also occurring with I50L. It is just a background that you would find with resistance to many PIs.

DR. GULICK: Dr. DeGruttola.

DR. DeGRUTTOLA: Actually, that was my question. For the patients that you showed in the naive study, where 100 percent of them had developed the I50L, I think you just answered it, that there is a variety of different types of mutations that they develop, but I was wondering if you can just expand on that a little bit more, basically, typical for proteases in general.

DR. COLLONO: I can actually, probably show you that. Go to D2, please.

[Slide.]

Again, this is just really comparing for a different reason, but it gives you the answer, I think, that you want, comparing the background for

responders, the ones that develop I50Ls and the ones that do not develop I50Ls when they become resistant.

Again, this is a subset of all the substitutions that we have looked at, but these are the ones that seem to have some differences between those three groupings. The only four mutations positions, at least with this particular analysis, that showed any kind of predictive nature, was an amino acid change at 14, usually 14R, that seemed to correlate with--you can see the green bar--seemed to correlate with I50L, the presence of a 46I also seemed to correlate, and also an 88D.

Then, on the opposite side, if you had a 90M, you tended to have the opposite relationship, so the 90M, you had less likelihood of getting the I50L. But apart from those mutations, there is really nothing different between the responders, I50Ls, and non-I50Ls.

DR. GULICK: Dr. Remmel.

DR. REMMEL: Given the durability, even with the I50L, do you have information on the fitness of the virus with just I50L mutants? You talked a little bit about an N88, which is a compensatory mutation to increase the fitness.

DR. COLLONO: Yes, we can talk about fitness. Just give me one second here.

As you point out, we have done this different ways. Of course, we have done it more traditionally with just drawing the virus and seeing what the fitness is, and then, in addition, we have actually gotten data from ViroLogic on a number of these isolates.

If I can have C10, please.

[Slide.]

Again, this is the more traditional growth curve, if you will. We took two clinical isolates with these backgrounds and put them into a recombinant clone, a laboratory isolate. The laboratory isolate is shown in green, and there is a normal growth curve over a period of days.

If you put in the number back, the 12 amino acids that we found as clinical isolate, you get the yellow curve, and the only difference is you put in the 50L and minus the 23, and you get this again, significantly growth-impaired virus.

Then, from the virologic data that we have, RCs, as you can see, we have this list here, but the vast majority of these, all but two, actually have an RC of 15 or less, so these are

significantly impaired viruses. We have never had a 50L-containing virus that seemed to grow like normal or in wild type virus.

DR. GULICK: Other comments from the committee on resistance in terms of using this drug in naive patients?

Dr. D'Aquila, can I put you on the spot to comment on that point?

DR. D'AQUILA: I would be happy to, Trip.

I think the data are promising. They suggest the possibility that not only will future treatment options be open to the naive patient who fails atazanavir, but the potential that the other drugs in this class might actually work better.

I think that remains to be proven. There are some preliminary data looking at viruses that are hyper-susceptible, increase susceptibility to amprenavir that were presented recently, in February.

There is also a couple of studies looking at non-nucleoside RT inhibitor, hyper-susceptibility, where in both of those situations, the viruses that had increased susceptibility in vitro, when that drug was used, there was a better viral load response than was seen against viruses

that had normal wild type susceptibility.

We just don't have that clinical data today, but I think I would expect that that is what you would see. Again, that is in the situation where this change in susceptibility leads to something greater than a 0.4 fold or I should say a number that is smaller than 0.4 in a shift in IC50.

I don't know what sort of effects will be seen if the I50L comes in a background where there is some other resistance mutations already present, and the I50L modulates the resistance downward, maybe not all the way to fully wild type virus.

That may not give us the same effect. There may still be resistance present although it is possible that even in the situation of decreased resistance, we will see some degree of improved responses, but I think the greatest potential is in the situation where you have, first, PI failure, and that introduction of I50L leads to increased susceptibility to other PIs, and potentially, you could follow up with a regimen that will work better than it would have worked otherwise.

DR. GULICK: Thanks.

Other comments on this population? Let's shift gears and talk about what did the resistance

data imply about the use of atazanavir in experienced patients. We saw lots of evidence for cross-resistance in the highly PI-experienced patient. Maybe we could also think about again atazanavir by itself versus boosted atazanavir.

Dr. Fletcher, why would a boosted ritonavir containing atazanavir regimen work better against a resistant virus?

DR. FLETCHER: Well, I think, to use the term from the sponsors, the PK cushion. You have an inhibitor that is going to raise the atazanavir levels, and in the case of viruses that have decreased susceptibility, it will provide the more typical type of relationship between the concentration of drug and the concentration that the virus needs to inhibit it.

I think it seems from a regulatory sense, I think the real issue is what type of information here do you try to communicate to the prescribers, you know, to the patients, to the individuals that are going to be using this drug, and beyond just those pharmacologic understandings now is when I totally have no expertise, but people talked about what a cut point might be, at least with the phenotypic assay.

I think I would leave it to others to comment on that, but that at least to me, there seemed to be some discrimination there in terms of responders and non-responders. I think that could be very, very useful information to convey somehow again to prescribers and to patients that would be taken the drug.

DR. GULICK: Dr. Kumar, can I pick on you and say, as a clinician, how are you going to use atazanavir in the experienced population based on resistance issues?

DR. KUMAR: I am struggling over that. As I have said several times before, I have a great deal of comfort in my naive patients, and in my mind, it is very clear that even if they fail, I have a part of where to go, but I am not that sure in the treatment-experienced patients, so I will stop right there.

DR. GULICK: Dr. Fish, can I pick on you, too?

DR. FISH: Sure. I think that the data that was presented by the sponsor, the issues come up more with three or more PI use, so I think, you know, just like we use with other drugs, we have some information in terms of what mutations are

going to confer decreased susceptibility and, you know, rapid utilization of genotypic testing and phenotypic when it is available to guide patients with resistance and determine whether or not it is a viable option, going be how we will use it in clinical practice.

So, I don't see that it will necessarily be a lot different and time will tell how many are susceptible and how many are not, but it seems to me it would be fairly similar as we use resistance testing to guide our treatment decisions currently.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: I think the dilemma is going to be what cut points are established by the companies that are doing a particular phenotypic testing because in the experienced patients, you are often dealing with patients who have resistance to most of the protease inhibitors and if this goes forward saying the cut point is 2.5, which somebody had mentioned earlier this morning, you know, that is not even in the same ballpark as some of the other clinically derived cut points for boosted protease inhibitors.

So, I think very clearly, more information needs to come forward on what are realistic cut

points, clinical cut points, in terms of initial loss of response and complete loss of response, you know, or major loss of response, because again in that setting, you are often having to choose among all poor options.

As I said earlier this afternoon, if you are trying to trade off toxicity, simplicity, lipid stuff with virological efficacy or effectiveness, having a more precise estimate of what the pharmacodynamic response pattern is in experienced patients is very important.

DR. GULICK: We have been struggling all afternoon with the issue of using atazanavir alone versus atazanavir/ ritonavir in the experienced population given the limited preliminary data that we saw in terms of efficacy, available safety data, and the available PK data.

Do people have some final thoughts about how that is kind of balancing out in their heads? Dr. Remmel.

DR. REMMEL: Again, I think this is where sometimes a pharmacokinetic evaluation could be helpful. If you had a 5-fold increase in resistance, and you have a patient with a longer half-life, you might feel more comfortable about

raising the dose slightly to make sure that you have a good therapeutic window.

Patients with shorter half-lives, you feel like you can't reliably raise that window. Because of a 24-hour dosing interval, you could go to a more frequent dosing interval or perhaps go to a boosted regimen. We haven't really talked about giving the drug on a BID schedule, but many patients could adhere to that schedule, and that might solve some of those problems.

So, it would just depend on what that ratio is. Again, if you are going to do this without any kind of guidance in terms of where your concentrations are, and you are just going to use phenotyping and genotyping, that may make some of those decisions more difficult to make.

DR. GULICK: Other thoughts about atazanavir versus boosted atazanavir in the treatment-experienced population given everything we have seen? Dr. Englund.

DR. ENGLUND: I don't think I can tell. I think in my patients, they are all going to have been exposed to ritonavir--the patients that I am going to be using it for, the most are going to be very treatment-experienced with ritonavir, so it is

going to limit some of the options I have.

I guess one of the things I would like to say is I would wonder whether any cut points should be on labeling as it is. I think the cut points are very test-dependent, they change over time depending on which company does it and who is going to be doing it two years from now, and which methodology they are going to be using.

I think that we, as a committee, should recommend that it be done prior to--I would recommend that it would be done prior to using it in the treatment-experienced patients, but I don't think we have enough data to be addressing that, and I also think the methodologies could change over time, so that is where I would be coming from.

I would be concerned about ritonavir-experienced patients when you are talking about the boosting issue.

DR. GULICK: Dr. Fish.

DR. FISH: I think we know that the first HAART regimen is the best chance, the second HAART regimen is the second best chance, so it will be tempting to want to use the ritonavir boosting, so you get long durability of that regimen, but it will also be a tradeoff in terms of the potential

side effects potentially into the impact on lipids that have been elucidated. They will come into play under those decisions, I think, as well.

So, I think the practice will be if the knowledge is out there and the information that this works and is the strategy. I think in clinical use, a lot of that will probably happen, i.e., boosting.

DR. GULICK: Other thoughts on that?

Okay. So, what did we say? First of all, as a committee, we have said that resistance testing is something that should be in the label, and that has been true of the last couple of approved drugs, that we do find it helpful.

Dr. Englund's concerns about making cut points too early without validated data is a caution to that.

In terms of the impact of what we have seen about resistance data on the naive population, I think we find this signature mutation story intriguing, but we would like to see some clinical data to show that sequencing of protease inhibitors really has clinical value to do it, but it is an intriguing story.

In terms of the experienced population,

the point made before that this is a heterogeneous population with lots of different levels of experience that clearly we will want to use resistance testing here, that the drug likely has, well, we saw data to support that it has activity in people with one or two PIs, but as you increase the number of PIs and the number of mutations, cross-resistance does become an issue.

Then, we went back to our debate about boosted atazanavir versus atazanavir with differences of opinion, but some people leaning towards the boosted as being the optimal regimen in a highly treatment-experienced patient.

Then, the point that we made earlier today that the attractive features of the drug in naives are also attractive in salvage in terms of convenience, tolerability, and lipid profile.

The last question is recommendations for Phase IV studies. Luckily, we have been talking about these all day and I have been keeping a list, so let me just read through the list and then maybe we can prioritize them and say what we think might be the most interesting.

Some of the ones that we have mentioned over the course of the day - resistance studies,

clinical follow-up of people who fail with atazanavir as their first protease inhibitor and then go on to another protease inhibitor, is that of clinical benefit.

More studies on lipodystrophy long term, cardiovascular events long term, as well.

Let's see, dose reduction of bilirubin, I guess we sort of canned that idea earlier today and thought that that is not something we would like to see pursued.

Pharmacokinetic interactions with some important drugs. Some of these are already in progress, such as methadone. Other drugs mentioned over the course of the day, H2 blockers, rifampin, statins, fibrates, nevirapine, tenofovir in progress we heard, ribavirin, and interferon were some of the ones mentioned. There may be others.

Long-term safety was a recurring theme today, long-term follow-up of the bilirubin, liver function tests, and again cardiovascular complications and lipodystrophy.

More information on atazanavir boosted with ritonavir. Adherence information, pediatrics, longer term follow-up. More than once, pharmacokinetics particularly in terms of drug

monitoring as an explanation for virologic failure, TDM as a possible mechanism of that.

Mentioned more than once today was the issues about a QD regimen and might that put people at risk if they drop a dose on a QD regimen.

We heard from our cardiology consultants some debate about whether further preclinical assessment would be of interest in terms of QT and PR effects. Also, looking at more clinical expiration of that including the so-called worst case scenario.

Then, later on, markers of vascular inflammation was suggested by Dr. Illingworth on this way out the door.

Anything I missed in terms of Phase IV? Oh, I missed a lot. Drs. Englund, DeGruttola, and then Sherman.

DR. ENGLUND: Powder pharmacokinetics or powder or solution, not just for children, but certainly for older people G-tubes.

DR. DeGRUTTOLA: I don't think you missed this, I don't know if it was discussed, but I just want to raise the issue of doing more clinical studies of the relationship between genotype and clinical response in treatment-experienced

patients.

DR. GULICK: Dr. Sherman.

DR. SHERMAN: You know where mine will be. In the patients with more advanced liver disease, patients with cirrhosis and both compensated and decompensated cirrhosis, you have hepatically metabolized drug, and I think you need more data because we are seeing more and more liver disease in these patients.

The follow-on to that is that we are beginning to transplant patients with HIV, and we already know that several of the PIs have a huge interaction with FK and cyclosporin. We really, really need to know the interaction here, so that we can evaluate dosing issues in those patients, not just H2 blockers, but PPIs because of the issue of gastric acidity, and actually the PPIs are much worse than the H2s in terms of neutralizing stomach acid over extended periods of time.

The final one, not really so much a direct recommendation to the sponsor, but something to think about as we begin to raise the bar on liver issues is, you know, we have been using the sort of artificial surrogates of liver injury including the concept of Grade 3/Grade 4 toxicities for

management of patients with potential liver toxicity, in terms of deciding cutoffs.

We know that patients with much lower ALTs over long periods of time can manifest significant progressive liver injury evidenced by scarring in the liver, and therefore, if we are going to have agents that we are going to keep patients on for years, we need to be beginning to assess what happens histologically over extended periods of time in at least some of these patients.

DR. GULICK: Dr. Fletcher.

DR. FLETCHER: My comment in some way follows Dr. Sherman's. This is on drug interactions. So, there is not only a need, I think, for knowledge of whether there are some other interactions out there--and you ran through that list of those--but there is also, I think, a need for how you are going to manage some of these interactions.

Let me turn to a specific question, oral contraceptives. I am wondering if the sponsor has now some recommendation that they have thought about putting in a package insert about the management of that interaction.

DR. SCHNITTMAN: We have actually been in

discussions with the agency over this because of the increased levels. I mean, number one, we don't at least have to be concerned about loss of activity of the OCs, but there is the increased levels, and I think, as has been suggested already today at the meeting, using the lowest effective dose for that purpose would be appropriate. So, we will have further discussions with the agency on that.

DR. FLETCHER: I guess that gets to the question, what is that? Let me try to push you a little bit more. What would you propose to say in a package insert? So, here is the interaction between ethinyl estradiol and norethindrone. The levels of both are increased, so to say use the lowest effective dose, well, how do you know what the lowest effective dose is until it fails?

DR. SCHNITTMAN: Well, no, I mean I think the concern is on the up side there, you know, with the recent reports about long-term usage of these agents, and I think that is going to require a lot of thought about the appropriate wording on this, because this is a relatively recent kind of concern overall, I think that we haven't seen in labels before.

DR. FLETCHER: Just one more. So, that is my issue. I think that is not enough, at least for some of these interactions, to just say that there is an interaction there. I think some type of guidance to the clinician in what to do in terms of managing the interaction, I think is really necessary.

I think the additional issue that it seems to me you are going to have to work out is what do you say about ritonavir. If there is in the label, then, some mention of using boosted atazanavir, the drug interaction issues have to then talk, not only about atazanavir, but are going to have to talk about ritonavir interactions, as well.

So, it seems to me it adds a much greater degree of complexity in that section than I have probably seen before. I guess maybe it's like the Kaletra label, but there you don't have a choice. You get both drugs together and so there is not an issue of separating one or the other.

Here, there really is the issue of atazanavir interactions that can be separate then from atazanavir and ritonavir interactions, and I think, to me, this needs certainly more study, but probably also a lot more thought about how that

will get put into a label.

DR. GULICK: The agency has faced this before with amprenavir. How did you address that?

DR. BIRNKRANT: I don't think I can recall that at this point in time of the day.

[Laughter.]

DR. GULICK: Fair enough.

Dr. Remmel.

DR. REMMEL: While this isn't necessarily a Phase IV study, I think preclinically, there are a number of other drug interactions and effects on enzymes on CYP2B6, which is important for efavirenz and nevirapine metabolism. You had alluded to some inhibition of 2C9 and 1A2 and maybe getting a better definition of what those Ki's are, what the degree of inhibition is going to be.

We have a lot situations here where you write in the therapeutic range. You have got 2 micromolar for UGT 1A1, you have got 2.5 micromolar for 3A4, you have got 10 micromolar for the calcium channel, and you have got the mean Cmax at being about 4.5 micromolar, and concentrations are going to make a big change in terms of those drug-drug interactions. So, some maybe guidance in terms of banning also might be important.

I didn't see quite as much information as I would like in terms of each of those particular enzymes and what will be done there, but I think that would be useful to do.

DR. GULICK: Dr. Mathews.

DR. MATHEWS: I already mentioned the study that I thought should be done, a direct comparison of boosted versus unboosted for the lipid effect, but perhaps that could be studied in the context of another naive trial to look at boosted versus unboosted atazanavir to improve the long-term response rate, because as we have already commented on, for whatever reason, you know, 65 percent, whatever it was, suppressed at 48 weeks is not optimal obviously, so that is another study I think that could be considered.

DR. GULICK: Dr. Fish.

DR. FISH: I think it was Dr. Remmel's suggestion, but I think it is a great one, for the treatment-experienced patient, comparing boosted ritonavir with BID atazanavir, and most of the patients who are in highly salvaged situations are on twice-a-day regimens anyway.

DR. GULICK: How are we doing, Dr. Birnkrant, have we lived up to your expectations

here?

DR. BIRNKRANT: Exceeded them.

DR. GULICK: Great.

DR. BIRNKRANT: I have very high standards, so that is a plus.

DR. GULICK: Then, we will adjourn the meeting. Before I do that, I would like to thank the sponsor for their presentations, thank the agency also for their presentations, thank all of our committee members for hanging in there except the ones who left, and thanks to the audience.

[Whereupon, the meeting was recessed at 4:35 p.m., to reconvene the following day, Wednesday, May 14, 2003, at 8:00 a.m.]