FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

8:00 a.m.

Wednesday, January 8, 2003

Grand Ballroom
Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland

ATTENDEES

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TERRY PETERS, D.V.M.
JOHN POWERS, M.D.
C. GEORGE ROCHESTER, PH.D.
JANICE SORETH, M.D.

ATTENDEES (Continued)

AVENTIS PHARMACEUTICALS, INC. REPRESENTATIVES:

VIJAY BHARGAVA, PH.D.
STEVE CAFFE, M.D.
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EMANUEL RUBIN, M.D.
CRAIG PRATT, M.D.

ALSO PRESENT:

ITZHAK BROOK, M.D.

C O N T E N T S

NDA 21-144, Ketek (telithromycin),
Aventis Pharmaceuticals, Inc.,
Proposed for Treatment of Community-Acquired Pneumonia,
Acute Exacerbation of Chronic Bronchitis,
and Acute Maxillary Sinusitis

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C O N T E N T S (Continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. LEGGETT: Good morning. Welcome to this Anti-Infective Drugs Advisory Committee meeting regarding telithromycin, presented by Aventis Pharmaceuticals.

I think we will begin with introductions, and we'll go around the table, beginning with Ken Brown.

DR. BROWN: Ken Brown. I'm representing industry as a whole I guess. I haven't heard from anybody telling me any more detail than that.

DR. PORETZ: I'm Donald Poretz, an infectious disease practitioner in Fairfax, Virginia.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedars-Sinai and UCLA.

DR. RUPP: Good morning. I'm Mark Rupp, adult infectious diseases at the University of Nebraska.

DR. WALD: I'm Ellen Wald from the Children's Hospital of Pittsburgh, infectious diseases.

DR. BELL: David Bell, National Center for Infectious Diseases, CDC in Atlanta.

DR. MAXWELL: Good morning. Celia Maxwell, infectious diseases, Howard University Hospital.

DR. RELLER: Barth Reller, infectious diseases, and clinical microbiology Duke University Medical Center.

DR. O'FALLON: Judith O'Fallon, Cancer Center

Statistics, Mayo Clinic.

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

DR. LEGGETT: Jim Leggett, infectious diseases, Oregon Health and Sciences University.

DR. PATTERSON: Jan Patterson, medicine, infectious diseases, University of Texas, San Antonio.

DR. LEE: Will Lee, hepatology, UT Southwestern in Dallas.

DR. KLEINER: Dave Kleiner, laboratory pathology, National Cancer Institute.

DR. ROCHESTER: George Rochester, Office of Biostatistics.

DR. COOPER: Chuck Cooper, medical officer, Division of Anti-Infectives.

DR. ALEXANDER: John Alexander, medical team leader, Division of Anti-Infectives.

DR. SORETH: Good morning. I'm Janice Soreth, the Director of the Division of Anti-Infectives at FDA.

DR. LEGGETT: Thank you.

Tara, would you please help us with the conflict of interest?

DR. TURNER: Thank you.

The following announcement addresses the issue of conflict of interest with regard 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 for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Drs. Steven Ebert and John Bradley have been recused from participating in today's discussions and vote concerning Ketek.

In addition, in accordance with 18 U.S.C. 208(b)(3), the following individuals have been granted waivers permitting their participation in today's meeting.

Dr. Celia Maxwell has been granted a waiver for her consulting for a competitor on an unrelated matter. She receives less than $10,001 a year.

Dr. Ellen Wald has been granted a waiver for her consulting for a competitor on an unrelated matter -- she receives less than $10,001 a year -- and for her and her employer's participation in a trial funded by a competitor involving a competing product on an unrelated matter. This research is funded at less than $100,000 a year.

Dr. William Lee has been granted a waiver for his role as a consultant for a competitor on an unrelated matter. He receives fees of less than $10,001 for this activity.

Dr. Jan Patterson has been granted a waiver for her consulting for two competitors on unrelated matters -- she receives less than $10,001 a year from each firm -- and for her spouse's consulting for a competitor on an unrelated matter. He receives fees of less than $10,001 for this activity.

Dr. Donald Poretz has been granted a waiver under 21 U.S.C. 355(n)(4) amendment of section 505 of the Food and Drug Administration Modernization Act for his ownership of stock in a competitor valued between $5,001 to $25,000.

Dr. Mark Rupp has been granted a waiver under 21 U.S.C. 355(n)(4) amendment of section 505 of the Food and Drug Administration Modernization Act for his ownership of stock in a competitor valued less than $5,001.

A copy of the 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.

In addition, we would like to disclose that Dr. Kenneth Brown is participating in this meeting as an acting industry representative, acting on behalf of regulated

industry. Dr. Brown reports that he owns stock in Johnson & Johnson and Pfizer. Dr. Brown also serves as a consultant to Wyeth on an issue unrelated to that coming before the committee for consideration.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has 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 firms whose products they may wish to comment upon.

Thank you.

DR. LEGGETT: Thank you.

Let's begin today's proceedings with the historical background of Ketek. Dr. Soreth.

DR. SORETH: Good morning. I'd like to give a bit of an overview of the new drug application brought by Aventis for telithromycin, or Ketek, as this committee heard almost two years ago, efficacy and safety data in the first cycle of that review, a little bit more about the regulatory history and dates that surround that, an overview of the efficacy and safety data presented in April

of 2001, a few months later the FDA action letter that followed asking for additional studies with regard to safety and efficacy, and then a brief description of those studies.

The new drug application for telithromycin was submitted by Aventis first in February of 2000, and this Anti-Infective Advisory Committee met in April of that year to discuss the safety and efficacy data.

A few months later, the agency issued an approvable letter in June of 2001, outlining a request for additional studies to understand better the risk-benefit profile of the drug.

And Aventis submitted to the agency an amendment in July of 2002 with the data from those new studies.

In the meantime, the drug application had been approved in a number of European countries and Central and Latin American countries, and post-marketing exposure was also submitted to the agency.

Five-and-a-half months later, we're up to now.

In the initial application four indications were proposed: community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis, and tonsillopharyngitis. And for the first three infections mentioned, pneumonia, bronchitis, and sinusitis, the

company included proposed labeling that would include efficacy against penicillin- and erythromycin-resistant strains of Strep. pneumoniae.

In April of 2001, the clinical database in phase III at that time was comprised of about 13 trials with at least two controlled trials in each of the four indications requested and some uncontrolled trials in a few indications as well.

By way of sweeping review, because you're going to see this data and a lot more as the day unfolds, in CAP and bronchitis and sinusitis -- and I'll stop for a moment so that you can look at the slide more carefully -- efficacy rates tended to run in the 80s and 90s for telithromycin and comparator agents, and equivalence or noninferiority, by and large, was demonstrated for pneumonia, for acute exacerbation of chronic bronchitis, for sinusitis.

In April of 2001, we discussed briefly the results for a study in tonsillopharyngitis and at that point spoke to the primary efficacy parameter in this indication, being that of microbiologic eradication. There was a comparative study that compared telithromycin to penicillin with a success rate of 84 percent for teli and 89 percent for penicillin. And our guidance on this issue I think is fairly clear, that we look for at least a

success rate of 85 percent for a first line claim, and further discussion on this indication was then tabled.

With regard to the body of evidence in April of 2001 for drug-resistant Strep. pneumoniae, we looked at the following data. Overall over 170 cases of Strep. pneumoniae of any susceptibility, with a 96 percent success rate. Necessarily and usually the body of data for PRSP is smaller, 17 cases with a success rate in the 80s, and then a further subset of patients who were bacteremic with penicillin-resistant Strep. pneumoniae in the setting of community-acquired pneumonia, a total of 6 cases with a success rate of 67 percent.

Similarly for patients with pneumonia, due to erythromycin-resistant Strep. pneumoniae, these are not the exactly the same 17 cases. There's about a 50 percent overlap, but success rates were the same, in the 80s, in the 60s with a smaller experience for those who have concurrent bacteremia.

In summary, the agency analyses were really consistent with those of Aventis for pneumonia, bronchitis, and sinusitis. The discussion that ensued around the data took into account not only efficacy, but also the other side of the equation when we're considering drug approval, and that is safety.

Our segue to safety then is just that, and at

the time of April 2001, the database for Ketek included in phase III a little bit over 3,000 patients, about 2,000 in the setting of controlled trials for Ketek, another 1,200 patients in uncontrolled trials, together with various comparators and 1,700 patients' exposure.

There were no deaths in phase I trials. There were a total of 11 deaths then in phase III, primarily in community-acquired pneumonia, primarily in patients in higher risk categories, Fine category III or higher. None of the deaths were directly attributed to drug.

In 6 of the 7 telithromycin deaths, there was a cardiovascular cause listed as one of the causes of death, again none directly attributed to drug, compared to 0 out of 4 comparator agents who had a cardiovascular cause listed.

And with regard to serious adverse events in phase III, we saw the following. Equal numbers roughly in both arms overall, and small numbers of each of these cells for allergic reaction, liver damage, gastroenteritis, et cetera.

With regard to overall adverse events, the common adverse events are referable to the GI system, diarrhea, nausea, vomiting, whether one looks at telithromycin or the comparators.

Although uncommon, I just want to draw your

attention to the final line of blurred vision, uncommon overall in the database, but when we did see it, much more likely to be seen in the telithromycin arm versus comparators.

The focus of the advisory then was on three areas in the realm of safety: cardiac, hepatic, and visual. How did this come about? Well, we look first to animal data, in vitro data, to give us some indication of where to look, what might be the target organs potentially of toxicity.

Telithromycin inhibited IKr channels, prolonged action potentials in isolated fibers, and prolonged QT in dogs. The numbers are here. You'll hear more about this today. The effect is modest in phase I whether in young patients or in elderly, on the order of a few seconds of QT prolongation, a bit longer if one takes into account a CYP3A4 inhibitor.

In phase I, we discussed briefly nonlinear pharmacokinetics, with a mean Cmax after a single dose of 800 milligrams, on the order of 2 milligrams per liter; maximum Cmax, a little bit over 5 for those subjects who were renally impaired. Similar numbers for multiple dose exposure. And in phase III, the maximum observed concentrations ranged between 7-and-a-half and just under 10.

In elderly subjects, as well as subjects with renal impairment, Cmaxes and AUCs were higher, ranging from 30 percent greater up to 100 percent. In patients with hepatic impairment, area under the curve and Cmax were quite similar to healthy subjects, as long as renal clearance was normal. Although there were not specific data at that time to speak to it, we raised the question of potential accumulation if creatinine clearance was reduced in the setting of hepatic impairment.

In phase III, telithromycin had a small but consistent increase in controlled trials. And I recall at that time, in Dr. Ruskin's presentation in general on matters of QT and drugs that can affect cardiac repolarization, the idea that in the setting of noncardiac drugs that can have a small or modest effect on cardiac repolarization, it is extremely rare to see clinical problems in the setting of healthy subjects on that drug alone. Rather, the concern raised in the setting that we have historically in the agency sometimes seen problems is the setting where there's increased exposure of the drug that can have a modest effect on QT and some perturbation, comorbid conditions, drugs that compete for cytochrome P450 isoezymes, states that for one reason or another increased exposure that may then lead to problems, necessarily painting a picture that there will be lots of other

conditions and things going on when one might see a problem that becomes a clinically significant problem with prolonged QT.

What about the hepatic body of data? Preclinically in the species tested -- dogs, rats, monkeys -- hepatotoxicity was noted by virtue of increases in transaminases and liver necrosis in a 4-week rat study. In phase I, there was a clustering of some hepatic adverse events in the elderly who were given a single supratherapeutic dose but no clear dose response for hepatic adverse events. And overall in phase III, similar rates of reported adverse events for hepatic issues, telithromycin versus comparators. No apparent drug-induced hepatic deaths.

There were, at the time of the April 2001 advisory, 2 hepatic serious adverse events possibly, plausibly associated with telithromycin, and there was at that meeting one liver biopsy discussed in a Finnish patient read as centrilobular necrosis, eosinophilic infiltration which could be consistent with a drug-induced picture. It could not be ruled out. We will see that case again today, as well as another liver biopsy review.

Overall in phase III, there were more AST and ALT elevations in telithromycin-treated patients in the pneumonia trials, not seen in non-pneumonia patients, and

concomitant low-level transaminase and total bilirubin elevations in telithromycin-treated patients.

Now to visual data. In phase I, about 4 out of 1,000 subjects reported blurred vision with supratherapeutic doses, and in phase III, 14 out of 2,000, a tiny percentage, versus 1 out of 1,600 in a comparator. The majority of patients were under 40 -- we'll say young -- and female. The report of blurred vision was usually transient but variable, minutes, days, hours. It was over the map.

In summary, the issues discussed at the April 2001 advisory about potential QTc prolongation, a concentration-dependent effect of telithromycin on QT, a concentration variation in special populations like those with hepatic and renal disease, those with comorbid conditions, potential for effects on the liver, raised questions of increased exposure in the elderly and those with concomitant medications and what effect that would have then on the safety picture.

There were limited data on subjects at risk, often the case because our controlled clinical trials are designed in such a way that we have exclusion criteria that sometimes give us not so much data when there are many comorbid conditions or concomitant meds. And we reviewed this data in the setting of a potential for wide population

exposure, for we know that in the United States each year we write many, many prescriptions for patients on an outpatient basis for those with respiratory tract infections like bronchitis or sinusitis or pharyngitis, prescriptions in the millions.

The vote taken at that time was on these questions. Do the efficacy and safety data presented support the use of Ketek, or telithromycin, in community-acquired pneumonia, bronchitis, sinusitis? The majority of you voted yes with regard to community-acquired pneumonia. The majority voted no with regard to bronchitis or sinusitis. The discussion that ensued around this was not one that questioned efficacy. Rather it was one that raised questions about risk-benefit overall and about a desire to have a better understanding of the safety profile.

With regard to drug-resistant Strep. pneumoniae overall, whether for pen-resistant isolates or erythromycin-resistant isolates, the majority of you did not feel that you had enough data to support the claim. You raised questions to some extent as well about the body of evidence available at that time to speak to the clinical impact of macrolide-resistant Strep. pneumoniae. We'll hear more about that today.

You made recommendations to us at that time

that included a desire for a larger number of patients to be enrolled in safety studies with particular attention to special populations being targeted like the elderly and patients with various organ impairment like hepatic impairment or renal and to have a better understanding of the pharmacokinetics in those populations, together with some more data on drug-drug interactions.

On the side of efficacy, you also recommended the gathering of more data in patients with drug-resistant Strep. pneumoniae, including hopefully those with bacteremia.

In June of 2001, we issued an approvable letter for community-acquired pneumonia, bronchitis, and sinusitis. We too asked for additional safety and efficacy data to assess risk-benefit.

Aventis worked with us in the Division of Anti-Infectives in the design of trials in phase I and phase III to gather those data.

In phase III then, study 3014, about which you'll hear quite a lot throughout the day, was a randomized, open-label, multi-center trial that compared telithromycin to amoxicillin-clavulanate in outpatients who could enter with either pneumonia, bronchitis, or sinusitis. This was a trial designed to simulate the usual care setting. It's a big study. It's a big effort.

24,000 patients were enrolled. It was designed as a large safety study to look at adverse events of special interest, namely cardiac, hepatic, and visual.

In addition, other phase III studies were conducted to address a request for additional efficacy data in community-acquired pneumonia on drug-resistant Strep. pneumoniae. You'll hear the results of these studies as well.

And finally in phase I, studies were conducted to examine cardiac issues and QT interval changes when the system was taxed, when the deck was stacked, with regard to patients having renal impairment and receiving telithromycin or having renal impairment and receiving telithromycin as well as ketoconazole.

In the visual realm, studies were designed to enable extensive ophthalmologic evaluation in both young subjects, as well as older subjects, in the setting of single doses, multiple doses, crossover designs, looking as well at pharmacokinetics of telithromycin in plasma and tears.

And finally in the setting of phase I studies referable to what was going on with the liver, there's a multiple dose study of telithromycin in patients with hepatic impairment versus healthy subjects.

As of October of 2002, there were 1 million to

1.5 million exposures in Europe and Latin America of telithromycin; in Europe, largely in Germany and France.

In closing, I wish to tell the committee that we get very excited in the division when given the opportunity to review a new class of drugs. We recognize that the pipeline for antibiotic drug development, for drug development of new chemical entities is not overflowing, and I want to recognize, applaud, and thank Aventis for a great amount of work that's been done in the endeavor to develop a new compound for the treatment of respiratory tract infections.

There is the potential to increase our armamentarium of agents to treat respiratory tract infections, including resistant pathogens. I think that's important. At the same time, with opportunity always comes challenge. And in the review of any new drug application, maybe especially in the setting of development of a brand new class, a first in a class, one also has to carefully examine data to speak to potential toxicities.

With regard to risk, I'd like to read a very brief passage from a book written by Peter Bernstein, Against the Gods: The Remarkable Story of Risk. The ability to define what may happen in the future and to choose among alternatives lies at the heart of contemporary societies. Risk management guides us over a vast range of

decision making, from waging to war to planning a family, from paying insurance premiums to wearing a seat belt, from planting corn to marketing corn flakes, from allocating wealth to safeguarding the public health.

He goes on to say that the scientists who developed the Saturn V rocket that launched the first Apollo mission to the moon put it this way. And this is a quote from Arthur Rudolph. You want a valve that doesn't leak and you try everything possible to develop one. But the real world provides you with a leaky valve. You have to determine how much leaking you can tolerate.

We ask the committee today to listen carefully to all of the data that will be presented with regard to safety and efficacy and to assess in the balance overall risk-benefit for telithromycin in the setting of what we anticipate would be wide exposure, wide usage.

And with that, I will thank you and turn the microphone back over to Dr. Leggett.

DR. LEGGETT: Thank you, Dr. Soreth.

Before I ask anyone if they have any questions, Alan, could you please, for the record, introduce yourself?

DR. CROSS: I'm Alan Cross, University of Maryland at Baltimore, Center for Vaccine Development, a new address.

DR. LEGGETT: Thank you.

And I noticed Dr. Goldberger there too.

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

DR. LEGGETT: Thank you.

Are there any questions for Dr. Soreth before we move on? Yes.

DR. ELASHOFF: Since I haven't been on anti-infective panels before, I wanted to clarify whether that 85 percent rule which was applied to decide that we weren't going to go for one indication, that that does not apply to the other three or it would apply to the other three?

DR. SORETH: No, it does not apply to the other three.

DR. ELASHOFF: It does not apply. So those could be less than 85 and one would still be interested.

DR. SORETH: Yes.

DR. ELASHOFF: Thank you.

DR. LEGGETT: Any further questions?

(No response.)

DR. LEGGETT: Thank you, Dr. Soreth.

Dr. Powers, could you please talk to us about the clinical significance of macrolide resistance?

DR. POWERS: Today I'd like to talk to you about, in asking a question really, what is the public health impact of macrolide-resistant Streptococcus

pneumoniae? And this is one of those experiences, when you look through the medical literature, that's very humbling in that sometimes what we think we know we don't really know and the more you read about it, the less clear sometimes something becomes. So I'd like to present to the committee today the information on the pros and cons of whether macrolide-resistant Streptococcus pneumoniae is an organism of public health importance at this point in time.

What I'd like to do first is present you some information on background on drug development for resistant pathogens that's been occurring within the last year and then discuss the body of information that's in the literature currently on the potential public health implications of macrolide-resistant Streptococcus pneumoniae. What I'd like to go through is some characteristics that we've come up with with an organism that would be considered of public health importance that is resistant to antimicrobials and then review those characteristics as they relate to macrolide-resistant Streptococcus pneumoniae.

It's important to realize today there are two separate questions here. The first one, as Dr. Soreth said, is is Ketek safe and effective for the indications for which it's seeking approval. The second related, though really separate question, is should Ketek, or any

other drug for that matter, garner a claim against macrolide-resistant Streptococcus pneumoniae based on what we know about this organism at this point in time. So the first question that we really have to tackle is whether macrolide-resistant Streptococcus pneumoniae is an organism of public health importance from what we know right now.

Several sponsors have requested indications for macrolide-resistant Streptococcus pneumoniae in the recent past but no drug has received that indication to date based on the agency's feeling that the information out there on this drug wasn't adequate at that point in time. But we're bringing that up again today to ask the committee whether they think the time is ripe to address this.

We've had several meetings addressing drug development for resistant pathogens in the last year. One was almost a year ago to this very advisory committee, and then one was more recently on November 19th and 20th this year in a workshop cosponsored by the agency, the Infectious Disease Society of America, and PhRMA. And at that meeting, members of industry and IDSA requested us to develop a list of resistant pathogens for which there is a public need for drug development.

Now, the public health importance of various organisms may vary over time based on changing epidemiology of the infections and the availability of alternative drug

therapies. For instance, in the mid-1940s, penicillin-resistant Staphylococcus aureus was considered a huge problem because the only drug available to treat it was penicillin. However, with the advent of vancomycin and then methicillin after that, one might consider penicillin-resistant Staph. aureus as not of great importance today but replaced by methicillin-resistant Staph. aureus.

So at that meeting in November, we discussed what we would consider the seven criteria or characteristics of a resistant organism that would characterize it as being of public health importance from a drug development point of view.

The first would be the incidence or prevalence of those organisms in the disease in question.

The second would be the virulence of the organism in question.

The third would be is resistance to the drug that we're talking about a drug commonly used to treat infections in the population under study.

The fourth would be are there available alternative therapies for the disease besides the drug that we're talking about.

The fifth, related to that, is are the organisms resistant to multiple drug classes, and that's a little separate than that in that sometimes we'll talk

about, say, resistance of Strep. pneumo to chloramphenicol. However, chloramphenicol really isn't used that often to treat Streptococcus pneumoniae.

The sixth is something recommended to us by our colleagues at the CDC which is, is the drug an essential component to prevent spread of the organism in the population. Just to give you an example of what this would mean, something like Neisseria gonorrhoeae infections where there is no vaccine currently and the actual drug is used to prevent the spread from person to person.

And then finally, the correlation of in vitro resistance with actual clinical failures.

What we talked about in November was there are some very clear-cut cases of organisms which fit these criteria such as methicillin-resistant Staph. aureus, vancomycin-resistant enterococci, and penicillin-resistant Streptococcus pneumoniae for which the FDA has already granted indications to drugs out there on the market.

However, less clear-cut was macrolide-resistant Streptococcus pneumoniae, and we asked this question directly in November and didn't get a whole lot of information there. So that's why we're bringing it up again today.

So let's apply these seven criteria then to macrolide-resistant Streptococcus pneumoniae and see what

we know. What, again, I would like to do and finally get to at the end is to present both sides of this issue so the committee can help give us some advice.

The prevalence of macrolide-resistant Streptococcus pneumoniae is clearly increasing, and in an active surveillance study done by the CDC from invasive isolates from eight counties and Atlanta, from 1994 to 1999 the prevalence of this organism went from 16 percent to 32 percent. So it doubled over time.

There are two types of resistance to macrolides in Streptococcus pneumoniae, as I'm sure you'll hear more about in the Aventis presentation. The one is the mefE mutants which is a gene that codes for an efflux pump. The other is the ermAM resistance gene which codes for a ribosomal methylase. In this study from Atlanta, they showed that the level of ermAM resistance remained stable through the 1994 to 1999 period, and almost all of the increase in resistance was made up by the mefE mutants.

However, the MICs for the mefE resistant isolates increased as well over time, from 21 percent with an MIC greater than 8 in 1995 to 94 percent with an MIC greater than 8 in 1999. And 63 percent of those had an MIC greater than 16 micrograms per milliliter. So we're also seeing, even amongst those mefE's, the MICs went up over time.

In a more recent study here, the epidemiology of MRSP from over 1,500 isolates in 33 medical centers across the U.S., so giving us a broader look at this, in a more recent time period from 1999 to 2000, showed that the MIC50 for these organisms was around .06 micrograms per milliliter. The MIC90 was 8, with a range that went all the way up to 64. .5 percent of those were considered intermediately susceptible to erythromycin based on the current National Committee for Clinical Laboratory Standards breakpoints. 25.7 percent of those isolates were considered highly resistant to erythromycin. But they did find that the rate of resistance, much like penicillin-resistant Streptococcus pneumoniae, was highly variable depending upon geography, ranging anywhere from 4 to 44 percent of the isolates.

So this raises very two related questions. The first is if we're going to call something susceptible resistance, how is this resistance defined in vitro. And the second question then is related. Is the population with invasive disease, such as that studied in the Atlanta study, the same population that would be treated with oral antimicrobials on an outpatient basis?

There's been some controversy over the breakpoints for macrolides, and I probably shouldn't say controversy except to say that they've been changing and

sometimes most recently. Before 1996, the NCCLS breakpoints for erythromycin were between 1 and 4 for intermediate strains and greater than 4 for resistant strains. After 1996 based on this paper by Jorgensen, the NCCLS changed the breakpoints to .5 for intermediate strains and greater than 1 for resistant strains, to bring them more into line with what was seen for clarithromycin at the same time.

However, some authors in the literature have argued that the breakpoints should be higher than this or the breakpoints should be lower than this. Some of the arguments that have been raised for raising the breakpoints have included that, in this study by Gerardo, 31 percent of isolates, when compared by E test versus broth dilution, had different MICs by sometimes up to eight-fold. An incubation of the organisms in ambient environments as compared to 5 percent CO2 lowered the MICs by one or two dilutions, making it look like an organism that had an MIC of 8, really had an MIC of 4 when incubated in air instead of CO2.

An older study done in 1988 showed that mixing 50 percent human sera in the media lowered the tube dilution sometimes again by up to 8-fold. So, again, an organism which may look like it had an MIC that was 8 sometimes came out to look like it was 2.

Also other studies, which we'll talk about in a little more detail, show that the pharmacokinetics of macrolides which concentrate the drugs in the white blood cells and the endothelial lining fluid really deliver more of the drug than what we see in the serum. Therefore, the breakpoints based on just serum levels alone would not be appropriate.

On the other side of this argument, however, other authors have claimed that the pharmacodynamic parameters of these drugs from animal studies show that the breakpoint should be as low as .5 to determine resistant organisms.

The second question then is, is the population that harbors these resistant organisms really the one that would be getting these antibiotics? And guidelines recommend oral outpatient therapy for patients with mild disease, less than the age of 60, and no comorbidities. According to the Pneumonia Outcome Research Trials, or PORT studies, these are people who fall into class 1 or class 2 of the pneumonia severity index as defined by those studies.

However, the risk factors for macrolide resistance in adults in this one study from Spain show that age of greater than 65 years and multiple comorbidities were the major risk factors for harboring a macrolide-

resistant organism, which would put a person in class 3 or above based on those things.

Other studies, however, show that age less than 5 years, isolates from the middle ear or the respiratory tract, prior antimicrobials, and also nosocomial acquisition are also risks. So although we see these organisms in patients greater than 65 with multiple comorbidities, they also occur in patients on the outpatient side who are less than 5 and get these bugs in their respiratory tract.

The second issue is the virulence of the organism. Streptococcus pneumoniae is clearly a virulent organism and can cause very serious invasive disease. However, to look at this another way, several studies show an inverse relationship of invasive disease with antimicrobial resistance. In other words, the resistant organisms are less likely to cause blood stream or CSF infections.

Also, outpatient mortality from community-acquired pneumonia is low, with the class 1 patients having a .1 percent mortality and the class 2 patients having a .6 percent mortality.

And several other studies show that the major risk factors for dying from community-acquired pneumonia have more to do with age and comorbidities than they do

with the actual resistance pattern of the organism.

Are macrolides commonly used to treat these kinds of infections? Well, they certainly are. Macrolides are used to treat mild to moderately severe community-acquired pneumonia, and in one study that was based on the PORT data, 62 percent of outpatients who had no comorbidities and were less than the age of 60 received a macrolide as their sole therapy for community-acquired pneumonia.

However, on the flip side of this, macrolides are rarely used as sole therapy in severe community-acquired pneumonia. In this study from Spain, although 62 percent of hospitalized patients received a macrolide, all of them got it in conjunction with a cephalosporin and none of them received the macrolide alone.

Other studies showed that only 2.5 percent of inpatients in this country received a macrolide as sole therapy for their community-acquired pneumonia if they were hospitalized.

And also macrolides are not used to treat severe disease associated with community-acquired pneumonia such as meningitis.

Are there alternative therapies for macrolide-resistant organisms? Well, some macrolide-resistant organisms are also resistant to other drug classes used to

treat pneumonia. 15 percent of macrolide-resistant Streptococcus pneumoniae are highly resistant to penicillin, and this is an interesting question. It depends upon how you look at it and what you start with. If you look at penicillin-resistant organisms, the majority of those are macrolide-resistant, but at least by this study from Gay done through the CDC, only 15 percent of macrolide organisms are penicillin-resistant, looking at it the other way. And another 19 percent of these macrolide-resistant organisms are intermediately susceptible to penicillin.

The question, though, remains based on data looking at penicillin and cephalosporin treatment of these patients, that the data imply that third generation cephalosporins and high-dose penicillin may still be effective for many of these penicillin-resistant organisms even with MICs up to or greater than or equal to 4.

So the question then comes up of are there actual data to indicate that patients will fail therapy more often with macrolides for macrolide-resistant Streptococcus pneumoniae, and we'll get to that in a little bit.

Continuing on with cross resistance to other drugs, for more recent data from the Doern study, for PRSP organisms, 77.8 percent of them are macrolide-resistant as

well, and penicillin resistance also predicts resistance to clindamycin in a quarter of those patients, tetracyclines in almost half, and 94 percent of those PRSP isolates are also resistant to trimethaprim-sulfamethoxazole.

On the flip side of this, this Doern study doesn't present starting off with MRSP and them looking at PRSP. So going back to the Gay study, remember that only 15 percent of MRSPs are PRSPs as well.

So the real question here is, are we even calling these drugs the correct thing? Are penicillin-resistant Streptococcus pneumoniae really more accurately called drug-resistant Streptococcus pneumoniae? And the question here comes up similar to vancomycin-resistant enterococci. Those organisms are almost all resistant to ampicillin and high doses of gentamicin as well, and yet we call them vancomycin-resistant enterococci, and yet, to date we haven't granted separate indications of vancomycin-resistant enterococcus, ampicillin-resistant enterococcus, and gentamicin-resistant enterococci. So does drug activity against PRSP accurately predict activity against MRSP and other forms of resistance as well based on this high rate of cross reactivity?

Then do we need drugs to control pneumococcal disease in the population. Well, the answer here is probably an easy one. It's probably not because 87 percent

of PRSP isolates are serotypes included in the 23 valent pneumococcal vaccine according to this data by Gay, and 66 percent of those isolates are serotypes included in the 7 valent vaccine as well. And it's predicted that these vaccines may result in a decrease in invasive disease.

Remember, however, that the resistant isolates are less likely to cause invasive disease. So the question remains, will the vaccine have a bigger impact on decreasing susceptible disease and less of an impact on decreasing resistant disease, given that these organisms cause less invasive disease?

Finally, we get to really where the money is, and that is, what is the correlation of in vitro results with clinical outcomes in patients who have macrolide-resistant Streptococcus pneumoniae infections? And this is the part that gets very humbling when you start looking through the data and trying to find information on this. There's really a paucity of data out there looking at this question.

There are almost no data on diseases other than community-acquired pneumonia. So that's where I'll concentrate the majority of my comments.

There are no reports on how patients do with acute bacterial sinusitis when they harbor resistant versus susceptible organisms.

There were few reports on patients with acute bacterial exacerbations of chronic bronchitis that show no increased failures in patients who harbor macrolide-resistant organisms. However, this is very complicated by the fact that the actual role of bacteria in acute exacerbations of chronic bronchitis still remains debatable, and even the impact of antimicrobial therapy versus no therapy is still a subject of debate as we talked about in November.

One study of group A beta-hemolytic streptococcal pharyngitis showed lower bacterial eradication rates with macrolide-resistant Streptococcus pneumoniae, 60 percent with resistant organisms versus 80 with susceptible, but no difference in clinical failures, with a 1.6 percent clinical failure rate in resistant organisms and 1.5 percent in the susceptible. Again, very complicated by the fact that it's unclear whether any antibiotic alters the course of your sore throat in group A strep pharyngitis. So these people might have gotten better anyway even though the drugs didn't work very well to eradicate the organisms. So the clinical outcome here doesn't really help us very much in this particular type of disease that has a very high spontaneous cure rate in any case.

So there are case reports or case-controlled

reports on failures of patients treated with macrolides who are infected with macrolide-resistant Streptococcus pneumoniae.

This one study by Kays included 32-year-old man who was receiving azithromycin and had a breakthrough bacteremia.

The study by Kelley includes 4 patients out of 41 in their hospital who received macrolides prior to coming into the hospital and then had breakthrough bacteremias.

The study by Lonks that was published last year in Clinical Infectious Diseases is a case-controlled study that looks at 18 patients who received macrolides prior who had macrolide-resistant Streptococcus pneumoniae. They had a larger number of cases. I think it was 86 all told. However, the problem here again gets to be that people who get admitted to the hospital don't often get macrolides as sole therapy. So trying to pick out people who got macrolides who then failed is sometimes difficult even when you find people who have macrolide-resistant Streptococcus pneumoniae because they may be receiving concomitant cephalosporins or other drugs that may affect the outcome.

However, on the other side of this equation, there are case reports of successes of patients treated with macrolides who are infected with macrolide-resistant

Streptococcus pneumoniae.

This study published a couple of years ago by Moreno and colleagues showed that 4 of 6 patients who were infected with macrolide-resistant Streptococcus pneumoniae, 3 of whom were bacteremic, were cures.

A study by Vergis on IVA azithromycin compared to cefuroxime plus erythromycin showed that 1 patient who was infected with a macrolide-resistant organism with an azithromycin MIC of 8 was a clinical cure.

And this study by Gotfried in the Journal of Antimicrobial Chemotherapy showed a similar survival rate in patients with macrolide-resistant Streptococcus pneumoniae, of which there were 27 patients. 95 percent of them were cured. The macrolide-susceptible Streptococcus pneumoniae patients, of whom there were 41, 82 percent of these were cured. However, the information on what drugs these people received was not available in a large number of those cases.

So there are challenges in interpreting this data either way when looking at both the successes and the failures of patients who have macrolide-resistant Streptococcus pneumoniae infections. As you can see on that previous slide, there are usually very small numbers of cases. They're usually retrospective, uncontrolled, or case-controlled data. When you look through some of these

cases, when the information is supplied, some of these patients probably weren't appropriate for oral therapy in any case. For instance, in the Kelley study of those 4 patients, one of them was a 75-year-old man with renal failure and liver failure. That's probably not the kind of person you would have put on oral macrolide as an outpatient in any case.

The other thing that gets very complicating is, can the natural history of the disease or other factors explain these failures? We know from data from Robert Austrian back in the 1960s from the University of Pennsylvania that no drug has any effect on the course of pneumococcal pneumonia in the first 5 days of treatment. So if someone gets a drug and on day 2 they fail, is that because they had such severe disease they were going to fail any drug, or is it because that is a failure of that particular antibiotic?

And it's also very complicated by the inherent differences in patients harboring resistant organisms. So when we compare patients who have macrolide-susceptible organisms to macrolide resistance, there are inherent differences, namely based on age and comorbidities, between the patients who have those. So it's unusual to be able to compare 22-year-old healthy people with macrolide-resistant organisms versus 22-year-old people with macrolide-

susceptible organisms.

So what can these cases tell us? They tell us that failures do occur. But the more relevant question that remains unanswered is, are the failures more likely to occur in patients who receive macrolides for macrolide-resistant pneumococcal disease versus macrolide-susceptible pneumococcal disease?

Well, why would anyone even suppose that patients who have MRSP may still be clinical cures when treated with macrolides? And there's some information out there in the literature that tries to explain this.

The first is the concentrations in endothelial lining fluid and white blood cells may exceed the serum concentrations for macrolides. And at least for the mefE mutants, this may exceed the MIC of these organisms. However, for the ermAM mutants this still may not be able to exceed the MIC.

Also, the contribution of the host immune system in younger patients with no comorbidities may help them get better despite whatever antibiotic they have or the resistance pattern of the drug.

According to some authors, the clinically relevant breakpoints for macrolides may be higher than the current NCCLS standards, as we already discussed.

Why would one expect clinical failures in

patients with macrolide-resistant Streptococcus pneumoniae infections when treated with macrolides? Well, even though those concentrations in the white blood cells and the endothelial lining fluid are high, they still may not be high enough for some of the isolates, especially the ermAM mutants. The other question this doesn't answer is, although this may be adequate for intracellular pathogens, how does this impact on extracellular pathogens, of which the pneumococcus is one?

Also, several reports show poor lung tissue levels of azalides in health volunteers despite the high endothelial lining fluid concentrations. Others would argue that these are in healthy volunteers and once the people are infected and the inflammatory component kicks in, the white cells then mobilize into the lung and carry this high level of drug with them. So the question remains what's the important parameter to look at here. Is it lung tissue levels? Is it white blood cell levels? Is it endothelial lining fluid concentrations?

Some studies in immunocompromised animals show failure of bacterial eradication with macrolide-resistant Streptococcus pneumoniae organisms treated with macrolides. However, other studies in immunocompetent animals show a better eradication rate, although still lower than that with macrolide-susceptible organisms.

And finally, the breakpoint for macrolides based on pharmacodynamic parameters may actually be lower than the current NCCLS standards based on some authors.

So finally, what do we have here in the end result? Is this organism significant or not at this point in time? And there are arguments on either side, and this is why we'd like the committee's advice on this today.

On the pro side of saying yes, this organism is of clinical significance at this time is the fact that the rising MICs, even for the mefE mutants, are occurring at this point in time in the U.S. Macrolides are commonly used for community-acquired pneumonia, and macrolide-resistant Streptococcus pneumoniae may be resistant to other drug classes as well. And there are case reports of clinical failures in the literature with macrolide-resistant Streptococcus pneumoniae.

On the other side of the equation saying no, this organism is not of clinical significance at this point in time, is that the mefE mutants are the most prominent, about two-thirds in the U.S. today, of all the macrolide-resistant Streptococcus pneumoniaes, and some authors would argue that you can dose these drugs for cure based on the increased concentrations in the endothelial lining fluid and the white blood cells which exceed the MIC for some of these mefE isolates.

Also, if we look at the Gay data, if we just look at macrolide-resistant Streptococcus pneumoniae, only 15 percent of them are resistant to penicillin. So are there alternative therapies available for most of the MRSPs? If we look at it the other way of around, however, most of the penicillin-resistant organisms are macrolide-resistant.

And finally, there are no studies directly evaluating the impact of macrolide-resistant Streptococcus pneumoniae on outcome. However, can we reasonably expect to ever get this data based on the fact that macrolides are not used as sole therapy in severely ill patients, and in most clinical settings, one doesn't get the sputum culture or blood cultures on a young, healthy outpatient with no comorbidities who may happen to then get community-acquired pneumonia.

So in conclusion then, what we'd like to ask you today is, does the current body of information on macrolide-resistant Streptococcus pneumoniae support granting indications for any drug for this organism at this point in time?

Also, should this vary depending upon the indication based on the fact that most of the information that we know is about community-acquired pneumonia? We have very little on sinusitis at all. And there's the

question of what impact even of antibacterial therapy for anything is in acute exacerbations of chronic bronchitis.

Would granting claims for macrolide-resistant Streptococcus pneumoniae at this time affect physicians' prescribing patterns? So, in other words, if the FDA approves a drug for macrolide-resistant Streptococcus pneumoniae, will physicians then assume that this is important and start changing their prescribing patterns?

Given that there may be other treatment options for macrolide-resistant Streptococcus pneumoniae, is it appropriate for physicians to be changing their prescribing patterns at this point in time for macrolide-resistant organisms?

And then given the overlap between penicillin-resistant Streptococcus pneumoniae and macrolide-resistant organisms, does granting an indication for penicillin-resistant pneumococcus imply that the drug must be effective for macrolide-resistant Streptococcus pneumoniae as well? And this goes back to the question that I raised earlier for vancomycin-resistant enterococcus, we don't grant separate indications for all the other drugs to which it is resistant, and one could make the same case for methicillin-resistant Staph. aureus, that although we label it as methicillin-resistant, that organism is also resistant to a number of other drugs, but we don't grant

separate indications for each one of those.

So I'll stop at this point in time.

DR. LEGGETT: Thank you, Dr. Powers.

Are there any questions? Yes.

DR. PATTERSON: When you're using the term "PRSP," particularly with regard to calling it drug resistant Strep. pneumo, are you referring to nonsusceptible; i.e., MIC greater than .1 or fully --

DR. POWERS: No. Everything I said today I used as MICs of 2 or above, given the fact that it doesn't appear that people with intermediately susceptible Strep. pneumo have any difference in outcome. So I confined it to only the highly resistant ones.

DR. MAXWELL: Under the virulence, the studies that showed the inverse relationship to invasive disease with antimicrobial resistance, was it primarily in patients with no comorbidities or was it across the board?

DR. POWERS: They don't actually comment on whether they have comorbidities or not. Some of those are in hospitalized patients as well.

There's a debate about that as well. Even though you look at that, some people would claim that the organisms which then mutate and become resistant are less fit and are less virulent. However, when you look at the people who actually get invasive disease, their mortality

is no different, and sometimes higher, if they have a resistant isolate than if they have a susceptible.

So there are two ways of looking at that. Even though it looks overall that it's less invasive, once you get an invasive isolate with a resistant pneumococcus, it's not like you're less likely to die.

DR. LEGGETT: Dr. Bell.

DR. BELL: John, that was an excellent summary.

I also was interested in that statement you made about that the drug-resistant infections were less invasive. What I do know is that rates of drug resistance are higher in respiratory isolates than in invasive isolates. That's very clear.

Whether the converse can be said, I'm trying to think about that. The invasive isolates resistance patterns are determined in -- at least in the CDC study, these are population-based active surveillance in large populations. The studies of resistance in respiratory isolates to my knowledge tend to be sentinel sites, not population-based, sometimes research projects. And I just wonder if we know enough to make the flat statement that resistant isolates are less invasive.

DR. POWERS: Yes. I think the way to look at this is there are two ways of looking at it. There's looking at it from a population-based point of view. Those

studies are mostly from Spain where they take people that had an invasive disease and they look back at their risk factors. And then they say, in the people who had invasive disease, they were less likely to have a resistant pathogen, but in the individual patient, if you are infected, if you have a blood culture positive, you're not less likely to die just because the organism is resistant versus susceptible.

DR. LEGGETT: Dr. Cross.

DR. CROSS: John, excellent presentation.

I have a technical question. What is endothelial lining fluid and how is it obtained?

DR. POWERS: What they do is they obtain by bronchoalveolar lavage. They actually go down there and wash out the lungs and then back-calculate for the dilutional factor of, I think it's, 100 ccs that they put into the lung, and then also normalize that based on the person's blood urea nitrogen concentration to come up with this. So this is what's actually lining the lung. That doesn't tell you what the concentration of the drug in the actual lung tissue is. So it's sort of lining the alveoli, but not in the spaces itself.

DR. CROSS: But it's not intravascular.

DR. POWERS: No.

DR. CROSS: I mean, the endothelium is on the

inside of the --

DR. POWERS: No, not at all. So you've got really three things to look at here. You've got serum concentrations of the drug. Four things. I'm sorry. Serum concentrations of the drug, the actual tissue levels of the drug, the white blood cell concentrations of the drug, which may be very high compared to serum concentrations depending upon which macrolide or azalide you're looking at, and then the endothelial lining fluid concentrations. Which of those is the most important in determining outcome really remains to be seen.

DR. LEGGETT: Yes, Dr. Brown.

DR. BROWN: I agree this was a wonderful presentation. I was hoping, however, that it would be a little more instructional than rhetorical. And I wonder if you would answer your own question for us.

(Laughter.)

DR. POWERS: Okay. No, I won't answer them. If I could, I wouldn't be asking it up here then.

DR. BROWN: I had several questions. I would like you to answer. You must have some final opinion, and I would like to hear what that is.

DR. POWERS: I never have opinions.

DR. BROWN: Secondly, I had a question about the value that you attribute to the case-controlled and

single-case data that you reviewed for us.

And thirdly, on your last slide, would granting claims for MRSP affect prescribing patterns, my question is, is that the charge to the FDA? And I'm asking this as a sincere historical question. My impression is that your division is asked to make one single decision. For the claims which the manufacturer wants to present, have they made their case the drug is effective and safe, not whether they're going to alter or try to control prescribing patterns for physicians.

DR. POWERS: You're absolutely correct. That is not our job. Our job is not to regulate the practice of medicine. However, I think that's something important for you on the committee as practitioners to consider when you're thinking about this.

Mike Scheld asked me at this November workshop about one of the ways we could determine how important an organism was, of public health importance, was look at what drugs physicians are using for those. I asked him the question, isn't that kind of circular reasoning in that once a drug gets approved, aren't physicians going to think it's therefore an important organism and start changing their prescribing patterns. Which is the one that really drives what's going on? And I think that's an unclear question.

You're absolutely right. It's not a question for us to answer, but I still think it's one for you to answer as clinicians. But you're right. The level of evidence that we're looking at is does the drug work for that particular type of organism in that particular type of infection.

DR. LEGGETT: One final question. Dr. Rupp.

DR. RUPP: Kind of a follow-up to the question that Dr. Patterson asked. With regard to macrolide resistance, particularly in the case studies that you looked at in the case-controlled trial, did they break it down with regard to any level of in vitro susceptibility or with regard to mechanisms of resistance, mef versus erm?

DR. POWERS: I'm sorry. As far as which studies?

DR. RUPP: Any of the outcomes data.

DR. LEGGETT: The CID.

DR. POWERS: The case failures?

DR. RUPP: The case failures and the case --

DR. POWERS: Actually for macrolide resistance, it's really not that helpful to break it down into intermediate versus highly susceptible because almost all of them fall into the highly susceptible. At least in the U.S. today, only .5 percent of them are intermediately susceptible to macrolides. So it's almost not worth

talking about. In fact, the difference was 25.7 versus 26.1 or something when you look at that. So for macrolide resistance, unlike penicillin resistance where it's almost split down the middle, it doesn't make a whole lot of difference to split that up.

When you do look at the resistance, depending upon where those cases come from, the majority of the U.S. failures have mefE resistance patterns. Some of the ones from Spain have ermAM resistance patterns. If I total up all of the clinical failures, most of them are mefE, though, because most of them come from the U.S. So I think what you're going to see depends upon where you are since two-thirds of the isolates in the U.S. right now, regardless of whether you succeed or fail, are mefE resistance mutants.

DR. LEGGETT: Thank you, Dr. Powers.

I think we should move on now to the sponsor presentation, and the introduction will be made by Dr. Steve Caffe.

DR. CAFFE: Mr. Chairman, members of the advisory committee, members of FDA, ladies and gentlemen, good morning. My name is Steve Caffe and I'm from the U.S. Regulatory Affairs Department at Aventis. It is my pleasure to introduce the sponsor's presentation on Ketek, generic name telithromycin.

Ketek is a ketolide antibiotic derived from the macrolides.

The indications we are seeking are for the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute sinusitis.

As just Dr. Soreth just reviewed, Ketek was presented to this committee in April 2001, which led to the recommendation that additional safety and efficacy data would be needed, including efficacy on resistant strains of S. pneumoniae and safety in a greater number of patients, particularly the elderly and those with comorbid conditions.

In June 2001, an approvable letter was received for Ketek for the treatment of CAP, AECB, and AS.

We are very pleased to be here today to share with you the results of a large additional clinical program which was successfully designed in collaboration with the Division of Anti-Infectives and which has addressed all the concerns that have been raised. As presented earlier also, this program included pharmacokinetic studies in special populations, additional efficacy trials in CAP and AECB and a 24,000 patient safety study comparing telithromycin to amoxicillin-clavulanic acid in a usual care setting. This study, focusing on the detection of hepatic, cardiac, and visual and vasculitic adverse events, showed that the

safety of telithromycin is comparable to that of amoxicillin-clavulanic acid.

Ketek was approved in the European Union in 2001, and post-marketing data is available from the countries where it has been launched, mostly coming from France and Germany. As of December last year, more than 1.5 million exposures were seen, and these data, taken together, show that all the issues have been addressed and that the safety and efficacy of Ketek have now been confirmed with this very large experience. The presentation today will show that Ketek is an important new treatment option for respiratory tract infections in the community setting.

The presentation will go as follows.

Dr. Iannini, who was the principal investigator for the large usual care study, will discuss the medical need for a new anti-infective for the treatment of respiratory tract infections.

Dr. Jenkins will review the microbiology of telithromycin.

Dr. Leroy will present the clinical efficacy data, including the additional data on resistant strains of S. pneumoniae.

Dr. Bhargava will review the human pharmacology of telithromycin with emphasis on special populations, as

per the FDA's request.

And Dr. Lagarenne will present the clinical safety data to address the questions that have been raised at the last Ketek advisory committee meeting.

Dr. Iannini will then return to conclude.

In addition, several experts are here with us today who can assist the committee with questions and deliberations. Their expertise covers all the areas to be discussed. Full details of their titles and affiliations have been provided to the committee.

I will now turn the podium over to Dr. Iannini.

DR. IANNINI: Well, good morning, ladies and gentlemen.

I'll be presenting the medical need for a new anti-infective agent for community-acquired respiratory tract infections really from a clinician's point of view.

Clinicians want agents available that have a targeted spectrum of activity against the most common respiratory pathogens. These pathogens include common bacteria, atypical organisms, and now strains that have acquired antimicrobial resistance. And complete confidence in the spectrum of activity is important because the vast majority of ambulatory patients receive empiric therapy without the benefit of microbiological guidance.

High potency against Streptococcus pneumoniae

therefore is very important. Rapid microbial killing is also desirable, as are therapeutic choices that include concentration-dependent killing agents which allow for shorter durations of therapy.

Clinicians are concerned with the effects of broader than necessary therapy on the development of resistance in pathogens in other areas.

And safety is always a high priority for clinicians, as is acceptable patient tolerance.

In selecting empiric therapy for community-acquired pneumonia, the greatest concern is that the two pathogens with the highest risk of mortality, Streptococcus pneumoniae and Legionella, are reliably treated. The increasing level of resistance of Streptococcus pneumoniae makes this an important issue.

Additionally, clinicians want reliable efficacy in patients with risk factors such as clinically unsuspected bacteremia, advanced age, and comorbid conditions. Treating AECB also requires reliable clinical efficacy, as failure of initial therapy may result in the need for hospitalization.

The clinician's concern in selecting treatment for patients with acute sinusitis is to ensure that the organism associated with the highest frequency of serious secondary complications, Streptococcus pneumoniae, is well

covered.

Patient convenience and compliance are also important for optimal outcomes and are more probable with a short duration of therapy.

This diagram depicts the currently available agents. As you can see, virtually all, telithromycin, macrolides, amoxicillin-clavulanate, and the fluoroquinolones, have appreciable activity against the common pathogens, Streptococcus pneumoniae, H. flu, and Moraxella cattarhalis. Amoxicillin-clavulanic acid lacks activity against the atypical and intracellular pathogens. Telithromycin and the fluoroquinolones have activity against erythromycin and penicillin-resistant strains of Streptococcus pneumoniae, while the macrolides have some activity against penicillin-resistant strains of Strep. pneumo, and amoxicillin-clavulanic acid has some activity against strains that are resistant to the macrolides.

In terms of activity in other pathogens, telithromycin and the macrolides have some modest activity against non-respiratory Gram-negative rods, whereas there's appreciable activity of amoxicillin-clavulanate and the fluoroquinolones which does raise the concern of resistance development in this group of pathogens by some clinicians.

Now, the current status of antimicrobial resistance in Streptococcus pneumoniae is difficult to

determine and that's because survey data may overestimate rates of resistance. What is consistent and clear, however, is that there's a growing trend towards resistance to penicillin-like drugs and the macrolides. Resistance levels to fluoroquinolones are currently low overall but do have an upward trend. And local outbreaks of fluoroquinolone-resistant Streptococcus pneumoniae have occurred and may be associated with high local rates of resistance. Resistance to multiple drugs is now reported in approximately 10 percent of survey isolates. This trend suggests the useful life of some older agents may be diminishing.

What are the implications of increasing resistance? The higher MICs of the more resistant isolates of Streptococcus pneumoniae have resulted in the inability of some currently available and commonly employed agents to achieve drug concentrations or time above the MIC that are predictive of optimal clinical outcomes. This is a particular concern for isolates with MICs of 8 micrograms per ml or greater to amoxicillin, 16 or greater for the macrolides, and 4 or greater for fluoroquinolones. Reports of clinical failures are being published and reported with these commonly prescribed agents.

Despite the absence of controlled study data linking microbial resistance to clinical failure,

clinicians are asking the question, do the available agents meet all of our clinical needs? Treating patients with respiratory tract infections with antimicrobial agents that the pathogen is likely to be reported as resistant to is at best uncomfortable for practitioners.

The clinical implications of resistance are under considerable debate, as you've early this morning. Some current publications suggest there is an increase in mortality and an increase in the incidence of suppurative complications such as empyema. When isolates of Streptococcus pneumoniae exhibit high level penicillin resistance. Controlled studies of outcomes in patients receiving concordant versus discordant therapy for highly resistant Streptococcus pneumoniae in community-acquired pneumonia are sparse, and they're also limited by the inclusion of small numbers of highly resistant strains. To date they fail to show increased mortality related to resistance to beta-lactams.

Other outcomes such as length of hospitalization and secondary complications have not been extensively studied.

Similarly with macrolides, recent papers show a high likelihood of failure to prevent breakthrough bacteremia when macrolide therapy is used to macrolide-resistant Streptococcus pneumoniae when it causes

community-acquired pneumonia even when the mechanism of resistance is efflux, and many of these failures were patients who were started on macrolides in the community and then presented on day 3 to 5 with bacteremia.

Clinical failures with macrolides in non-bacteremic cases have also been reported.

Fluoroquinolone failures in subjects infected with strains that are either initially resistant or that acquire resistance mutations during therapy have also been reported. There is concern on the part of some clinicians of an increasing incidence of resistance mutations in isolates that are reported in the susceptible range because additional mutations on therapy could increase the risk of clinical failure. This concern is greater for the older, pre-8-methoxy-fluoroquinolones.

Clinicians want to be able to choose agents that have potent activity against the pathogens including those that are resistant to current drugs. They want rapid bactericidal agents and they want activity at the site they're treating and not elsewhere. They want reliable therapy for unsuspected bacteremia in the ambulatory setting. They want to be able to prescribe therapy that is most likely to be the greatest potential benefit to their patients. All of these factors create the need for a new antimicrobial agent for respiratory tract infections.

I'd like now to introduce Dr. Stephen Jenkins who will discuss the microbiological aspects of telithromycin.

DR. JENKINS: Good morning, ladies and gentlemen.

I'll be spending a few minutes today discussing several of the salient features of the microbiology of telithromycin. First I'd like to briefly describe the issues that I'll be discussing over the next approximate 10 minutes.

Telithromycin is the first of the new ketolide class of antibacterial agents. It's differentiated from the macrolides, from which it was actually derived, based on its dual binding mechanism. This enhanced binding to the bacterial ribosome has endowed the compound with a very focused spectrum of activity that encompasses all of the common community-acquired respiratory tract pathogens and does so without disrupting, to any significant degree, the usual enteric or anaerobic gastrointestinal flora.

Specifically, the drug demonstrates very good activity against Haemophilus influenzae, irrespective of beta-lactamase production; Moraxella cattarhalis, irrespective of beta-lactamase production; methicillin-susceptible strains of Staphylococcus aureus; Streptococcus pyogenes; and the atypical and intracellular pathogens,

including chlamydophila, or as we used to say, Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila.

Telithromycin is especially active against strains of Streptococcus pneumoniae, including the increasingly common macrolide-, penicillin-, and multi-drug-resistant strains, and unlike the macrolides demonstrates rapid, concentration-dependent bactericidal activity.

First, I will address the novel mechanism of action of this compound that clearly differentiates it from the macrolides. Telithromycin inhibits protein synthesis by binding to two specific sites on the bacterial ribosome, thereby interfering with elongation of the nascent polypeptide chains. Like all MLS class antibiotics, it interacts with domain V on the 23S ribosomal RNA at position A2058. But unlike the macrolides or clindamycin, it also binds strongly to domain II at position A752.

As a function of this dual binding, telithromycin is active against the vast majority of macrolide-resistant strains of Streptococcus pneumoniae. In fact, in the ongoing U.S. PROTEKT surveillance study, the MIC99 was 1 microgram per ml against macrolide-resistant strains of Streptococcus pneumoniae. This means that less than 1 in 100 clinical isolates exceed the

proposed susceptibility testing breakpoint for macrolide-resistant pneumococci.

On this slide, we've attempted to depict the novel binding of telithromycin diagrammatically. If the position A2058 is blocked either by methylation or is changed due to a mutation, it renders the macrolides and clindamycin, in effect, inactive against strains of Streptococcus pneumoniae. By comparison with telithromycin, because it has a binding site both at A2058 and at A752, methylation at that site or mutation at that site does not render the compound inactive, and in fact the drug remains active against these strains.

On this next slide, the current United States antimicrobial resistance data from the PROTEKT program are depicted geographically. PROTEKT is a very well-controlled surveillance program with both national and international arms. It identifies at the molecular level the genes that are responsible for antimicrobial resistance among strains of Streptococcus pneumoniae. High-level penicillin resistance is now demonstrable in every part of the United States, as is macrolide resistance, the orange bars. And although somewhat variable geographically, approximately 10 percent of all strains of Streptococcus pneumoniae in the United States are now multiply drug-resistant, defined as resistance to penicillin, the macrolides, the

tetracyclines, and trimethoprim-sulfamethoxazole.

On this slide, the overall current antibiotic resistance rates for very well characterized strains of Streptococcus pneumoniae are presented. Among over 10,000 isolates that were recovered in the United States in the 2000-2001 respiratory tract season and tested in the central laboratory, approximately a quarter were fully resistant to penicillin with MICs greater than or equal to 2 micrograms per ml. Of real concern, approximately one-third were cross-resistant to all of the macrolide class antimicrobial agents, 13 percent were resistant to clindamycin, 31 percent to trimethoprim-sulfa, and 22 percent to the tetracyclines, all compounds frequently used for treatment of respiratory tract infections in the outpatient setting.

Now, although admittedly higher than the rates that are observed among the isolates that were recovered during the past 5-plus years in the clinical trials performed by Aventis, if you take a look at the 3,700 blood culture isolates recovered in 2000-2001 in this surveillance program, 21 percent of those blood culture isolates were fully resistant to penicillin and 25 percent were fully resistant to the macrolides. This is consistent with the susceptibility results observed in the overall PROTEKT program.

Although still relatively low at 0.9 percent, resistance to the fluoroquinolones was observed in more than 80 isolates in this study, including 14 recovered from blood cultures. And telithromycin was active against every one of those isolates.

On this next slide, the in vitro activity of telithromycin against the common bacterial pathogens associated with community-acquired respiratory tract infection are presented. The compound is clearly highly active against Streptococcus pneumoniae with an MIC50 of only 0.015 micrograms per ml -- this is the concentration that would be expected to inhibit at least half of all clinical strains -- and an MIC90 of 0.5 micrograms per ml.

Telithromycin also has very good activity against Haemophilus influenzae, irrespective of beta-lactamase production; Moraxella cattarhalis, again irrespective of beta-lactamase production; Staphylococcus aureus for methicillin-susceptible strains. Telithromycin has very limited activity against methicillin-resistant strains of Staph. aureus. And finally, Streptococcus pyogenes, an organism that we see not infrequently in acute bacterial sinusitis, likewise the compound demonstrates excellent activity.

For Haemophilus influenzae, another important point to raise is the fact that this compound does

demonstrate concentration-dependent bactericidal activity unlike the macrolides such as azithromycin that demonstrate time-dependent bactericidal activity. In addition, as will be discussed by Dr. Bhargava in his presentation, the levels of telithromycin that are demonstrable in the epithelial lining fluid of subjects with respiratory tract infections, approximately 15 micrograms per ml, 2 to 3 hours after a standard 800 milligram dose, significantly exceed the MIC50 of 1 microgram per ml and the MIC90 of 2 micrograms per ml for Haemophilus influenzae. And likewise, the drug is significantly concentrated by the alveolar macrophages that are recruited to the site of the infection, with levels exceeding 300 micrograms per ml 10 to 12 hours after standard dosing.

As demonstrated on this slide, telithromycin also exhibits excellent activity against the atypical and the intracellular pathogens that are typically refractory to the beta-lactams in vitro and is particularly strong against strains of Legionella pneumophila. In addition, the MIC90 and the MCC90, which is the minimum chlamydicidal concentration, are identical for chlamydophila pneumoniae at 0.25 micrograms per ml.

Without dwelling on the actual MICs in any great detail, as is presented on this slide, telithromycin maintains its activity against macrolide-resistant strains

of Streptococcus pneumoniae, right here, whether it be due to methylation of the ribosome, the ermB strains, or efflux, the mefA strains. It is also active against strains that harbor both mechanisms of resistance, methylation and efflux. The compound is also active against essentially all penicillin-resistant pneumococci, fluoroquinolone-resistant pneumococci, and multi-drug-resistant pneumococci.

The distribution of MICs, as depicted on this slide, clearly shows that telithromycin retains activity against macrolide-resistant pneumococci, with MICs typically ranging from less than .015 micrograms per ml up to around 1 microgram per ml. By comparison, the MICs for all of the macrolides has shifted far to the right, with MICs frequently greater than 16 micrograms per ml. In fact, in this program when they went back and retested these isolates with MICs greater than 16, the majority of them actually had MICs in the range of 256 micrograms per ml, clearly far higher than the achievable levels for these compounds.

Importantly, approximately 59 percent of the isolates that were resistant due to the efflux mechanism were, in fact, highly resistant with MICs of 16 micrograms per ml or greater, and 69 percent of all of the blood culture isolates in this program that were resistant

because of efflux likewise had MICs of greater than 16 micrograms per ml, levels clearly non-achievable with the macrolides.

Similarly, unlike the Gay study in Atlanta where 15 percent of so of the macrolide-resistant strains were penicillin-resistant, 67 percent of the macrolide-resistant strains due to efflux in the PROTEKT program were also resistant to penicillin.

The bactericidal activity of telithromycin, even against strains of pneumococci that are resistant to the macrolides because of efflux or methylation of the ribosome, is demonstrated on this slide. Although strain-to-strain differences were sometimes seen, bactericidal activity was almost uniformly observed.

Finally, as described on this slide, telithromycin has been shown to have a low propensity to select for antibiotic-resistant mutants. In vitro telithromycin fails to induce MLSB resistance amongst the common respiratory tract pathogens, and in serial passage experiments has been shown to be less likely to select antiobotic-resistant mutants of Streptococcus pneumoniae than other MLS class compounds.

Telithromycin also demonstrated a lower propensity to select for mutants resistant to itself amongst the normal oropharyngeal flora, the viridans group

streptococci, than was clarithromycin in a controlled clinical trial. This is important since it's been shown that the resistance genes in Streptococcus pneumoniae have actually been picked up, including the mosaic penicillin resistance genes, through the process of transformation from these oropharyngeal viridans group streptococci.

In summary, telithromycin is the first of the new ketolide class of antibiotics.

Unlike the macrolides or clindamycin, it binds tightly to two different sites on the 23S ribosomal RNA.

It has a very focused spectrum of activity against the community-acquired respiratory tract pathogens and, unlike compounds such as the fluoroquinolones, does not significantly alter the normal Gram-negative or anaerobic gastrointestinal flora.

Telithromycin appears to select for resistant mutants at a very low frequency, has done so in animal models and in controlled clinical trial situations.

And finally, telithromycin is especially active against Streptococcus pneumoniae, the most common cause of infection in all of the indications being requested regardless of the organism's susceptibility or resistance to other antimicrobial agents.

Thank you for your attention, and I'd like to now turn the podium over to Dr. Leroy for his presentation

on the clinical efficacy of the compound.

DR. LEROY: Good morning. We will now review the clinical efficacy data.

14 clinical efficacy studies were performed with telithromycin in three indications: community-acquired pneumonia with a duration of treatment of 7 to 10 days except in a recent study where a 5-day treatment duration was investigated, acute exacerbation of chronic bronchitis with a treatment duration of 5 days, and acute sinusitis with a treatment duration of 5 or 10 days.

Elements of the study design were standardized across all indications in all studies, and the test of cure was performed between day 17 and day 21 at the same time after the study start in all groups. And this approach is very stringent since it allows the capture of early relapses in the test of cure, which is the main analysis. And this approach is also recommended by the FDA.

In studies with 5-day treatment duration of telithromycin, a placebo period of 5 days was added in order to maintain the blind.

In western countries, four double-blind comparative studies were performed in the indication of pneumonia, with a total of 1,583 subjects treated, 881 subjects treated with telithromycin 800 milligrams once daily for 5 to 10 days. Comparators included amoxicillin

high doses of 1 gram given three times daily for 10 days, clarithromycin 500 milligrams given twice daily for 10 days in two studies, and trovafloxacin 200 milligrams given once daily for 7 to 10 days.

In addition, 1,408 subjects were treated in four non-comparative studies, three of these referred as to enriched studies since the inclusion criteria were modified in order to increase the number of Streptococcus pneumoniae at inclusion and in order to increase the number of strains resistant to the macrolides or to penicillin G.

Data will also be presented on resistant S. pneumoniae from two studies from Japan, with a treatment duration of 7 days and a dosage of 800 or 600 milligrams once daily. And these include one dose comparison study and one comparative study versus levofloxacin given for 7 days.

In total, more than 2,500 subjects were treated with telithromycin in pneumonia in phase III studies, and we will see later that the clinical experience with strains of S. pneumoniae resistant to the macrolides has almost doubled to a total of 50 strains in this presentation.

On this slide, the bars represent the cure rates with telithromycin in blue and the comparators in gray, and at the bottom of the bars are the study numbers and the comparator used. At the top of the bars are the

cure rates and the 95 percent of the difference in cure rates between the two treatment groups.

The per-protocol clinical population was the population used for the primary analysis and will be used throughout the presentation. And results obtained in the modified intent-to-treat analysis, which excluded subjects with a clear misdiagnosis, were always consistent with the per-protocol data and are displayed in the briefing document.

Cure rates obtained with telithromycin showed that telithromycin was equivalent to high-dose amoxicillin and to clarithromycin in two studies, with telithromycin cure rates ranging between 88 and 95 percent, and a lower bound of the 95 percent confidence interval well within plan limits. Equivalence was also shown in the modified intent-to-treat analysis with a stringent delta of 10 percent.

Of note, in a recent study 4003, equivalence was also demonstrated between telithromycin given for 5 days and clarithromycin given for 10 days.

Study 3009 with trovafloxacin was stopped before the planned sample size was reached when the FDA restricted the use of trovafloxacin, but these results show an efficacy rate of 90 percent of telithromycin and also supports the efficacy of this drug in this indication.

In the telithromycin group, the clinical cure rate by pathogens for the targeted organism observed in our patients varied between 88 and 95 percent, with the highest cure rates observed for Streptococcus pneumoniae. Excellent efficacy was also shown for Haemophilus influenzae in this indication, and this was based on a large number of patients, over 200 patients.

For atypical pneumonia, stringent serologic criteria were used and no common pathogens were to be present in order for the patient to qualify for this diagnosis. The cure rates were over 90 percent for all atypical pathogens, and interestingly 13 subjects were diagnosed with Legionella infections for which early effective treatment is needed to avoid severe complications, and all those 13 subjects were cured.

On the next two slides, I'd like to show you the efficacy against the two main pathogens of the indication, Streptococcus pneumoniae and Haemophilus influenzae, according to telithromycin MIC.

Let's begin first with Streptococcus pneumoniae, the most important organism to consider in this indication. What we can see, as already stated by Dr. Jenkins, is that telithromycin is highly effective with outstanding in vitro activity against the strains of S. pneumoniae since the majority is below 0.016 microgram per

ml, and for the strains with an MIC over 0.25 microgram per ml, the clinical efficacy was excellent.

Now, when we look at Haemophilus influenzae, the key point I'd like to make here is that high bacterial eradication and clinical efficacy was observed up to an MIC of 8 microgram per ml.

Let us now examine the outcome in patients with resistant isolates of Streptococcus pneumoniae treated with telithromycin, and the results obtained in western countries and in Japan are presented on this slide.

We can see here that the efficacy rates are high both for penicillin-resistant strains and macrolide-resistant strains, over 85 percent, and the number of strains isolated in this program is high, with macrolide-resistant strains of Streptococcus pneumoniae with 50 isolates. With these 50 strains, this enables us now to evaluate the efficacy of telithromycin according to the genotype of resistance, and the main point here is that the efficacy appears similar in patients with an ermB, that is to say, MLSB mechanism of resistance, or with mefA strains, that is to say, efflux mechanism of resistance.

And of note, most of the strains with an MLSB mechanism of resistance displayed a very high level of resistance to erythromycin, as expected, with MIC to erythromycin greater or equal to 32 micrograms per ml and

telithromycin was very effective against those strains.

As said earlier by Dr. Iannini, one critical attribute of an antibiotic to be used in the community setting in patients with pneumonia is the activity in subjects with pneumococcal bacteremia. And the numbers obtained in this clinical development program are now very substantial given that these were outpatients treated with an antibiotic given orally. Telithromycin was shown to be highly effective in the 82 subjects microbiologically evaluable, exhibiting an efficacy rate of 90 percent. And if we look at the subset of patients with resistant Streptococcus pneumoniae, five out of seven strains resistant to penicillin G were cured, and 8 of the 10 subjects with Streptococcus pneumoniae resistant to the macrolides were cured.

It should be noted that among the two failures that are displayed in this row, they are the same patients. One patient did have eradication of S. pneumoniae resistant to penicillin G and erythromycin A with sterile blood culture and clear clinical improvement, but this subject was classified as a failure because of a secondary infection due to Staphylococcus aureus.

In addition, 4 other subjects had a sputum positive with macrolide-resistant strains of S. pneumoniae and a Binax antigen soluble urinary test for S. pneumoniae

positive. And all those 4 subjects were cured. This is important because for some authors it has been considered as a surrogate of a systemic infection in subjects with a negative blood culture.

Given the expected low rates of resolutions and the risk of complications and even death in patients with untreated pneumococcal bacteremia, these results clearly strengthen the proof of efficacy of telithromycin against strains of Streptococcus pneumoniae resistant to the macrolides.

What is important to consider in the outpatient setting is the population of subjects with underlying diseases or criteria of severity which are more prone to develop severe complications. And telithromycin was shown to be highly effective in the elderly in subjects with pneumococcal bacteremia and in subjects with a Fine score greater or equal to 3. This is based now on a substantial number of subjects when we pooled all the data from the pneumonia studies.

In summary, telithromycin given 800 milligrams once daily for 7 to 10 days was highly effective in community-acquired pneumonia. High cure rates were obtained for the key pathogens isolated in outpatients, both common pathogens, including also ERSP and PRSP, and atypicals including Legionella pneumophila. And efficacy

was also shown in the most vulnerable patients, that is to say, elderly and patients with pneumococcal bacteremia.

I will now present the results obtained in the acute exacerbation of chronic bronchitis. Three randomized, double-blind, controlled comparative studies were performed, including over 1,200 subjects treated, 612 treated with telithromycin 800 milligrams given once daily for 5 days. And the comparators were amoxicillin-clavulanic acid 500 milligrams given three times daily for 10 days, cefuroxime axetil 500 milligrams given twice daily for 10 days, and clarithromycin 500 milligrams given also twice daily for 10 days.

Patients enrolled in this study had a history of chronic bronchitis as per IDSA guideline definitions, and in study 3003 versus amoxicillin-clavulanic acid, all subjects were to have a documented bronchial obstruction at entry.

In addition, patients were enrolled with at least two or three criteria of exacerbation which are the most established Anthoniesen criteria used to identify patients who benefit from antibiotic treatments.

In the per-protocol clinical population, the clinical cure rate after the short 5-day treatment with telithromycin was equivalent to the longer 10-day treatment with the comparators used: amoxicillin-clavulanic acid,

cefuroxime axetil, or clarithromycin, all given for 10 days two to three times daily. Noninferiority was also demonstrated with a delta of 10 percent in all those three studies in the modified intent-to-treat analysis, which is also displayed in the briefing document.

In this indication in which the outcome is highly related to the underlying condition, the cure rate for the key pathogens ranged from 73 to 93 percent for clarithromycin and 79 to 85 percent for the comparator groups. For telithromycin, the cure rates were slightly better for Streptococcus pneumoniae and Moraxella cattarhalis, but also telithromycin exhibited a 90 percent cure rate in patients diagnosed with Chlamydia pneumophila infections which seems to play a role in the progression of the obstruction in this indication.

We've also verified that telithromycin was effective in the outpatients most likely to develop complications in this indication and cure rates were around 80 percent and similar to the active comparators in elderly in subjects with morbidity risk factors and in subjects with a significant bronchial obstruction.

To summarize, telithromycin 800 milligrams once daily for 5 days is effective in the treatment of acute exacerbation of chronic bronchitis in patients requiring antibiotic treatment, that is to say, patients with two

Anthoniesen criteria of exacerbation and with a spectrum targeted to common respiratory pathogens, including also Chlamydia pneumoniae. Efficacy was demonstrated also in the outpatients most likely to develop complication, in particular the elderly and patients with a significant bronchial obstruction.

Let us now turn to the efficacy data obtained in acute sinusitis. Three randomized, double-blind studies were performed to support this claim, comparing telithromycin 5 days with telithromycin 10 days, each given 800 milligrams once daily, and this study was performed in patients with total opacity or air fluid level in their sinus x-ray and all subjects had a sinus puncture for bacterial documentation at entry. 5 and 10 days telithromycin with 10 days treatment with amoxicillin-clavulanic acid given 500 milligrams three times daily for 10 days, and 5 days telithromycin with cefuroxime axetil 200 milligrams given twice daily for 10 days. And this study also included bacterial documentation at entry in outpatients.

In the comparative studies, equivalence was demonstrated between telithromycin given for 5 days and the two standard treatments in this indication, amoxicillin-clavulanic acid and cefuroxime axetil, each given for 10 days. And cure rates after the 5- or the 10-day

telithromycin evaluated in two studies were also shown to be equivalent.

Clinical cure rates for all targeted pathogens were high and comparable for the 5-day treatment, 10-day treatment with telithromycin, with rates over 85 percent for Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, as well as Staphylococcus aureus, in fact, frequently isolated in this indication.

Looking now at the experience obtained with Streptococcus pneumoniae resistant strains in the sinusitis trial, the first point I would like to make is that the macrolide-resistant strains were at a higher rate, above 30 percent, in the sinusitis clinical trial in the U.S. centers.

And I will focus first on the population of patients pooled from the 5- and 10-day treatment duration treated with erythromycin, which are displayed on the right of the table. 11 out of 13 strains penicillin-resistant were cured and 18 out of 21 cases with strains resistant to the macrolides were cured. Effectiveness was also shown in the 5-day group with rates over 85 percent in patients with macrolide-resistant strains.

Looking now at key subgroups in this indication, we note that in subjects with 7 days of symptoms or more or in subjects with a pathogen isolated at

entry, the efficacy of telithromycin was above 80 percent, and for subjects with signs of severe illness at entry or total opacity on their sinus x-ray at entry, the efficacy is also above 80 percent. And in all the subgroups, telithromycin had comparable efficacy versus the comparator treatments.

To summarize, telithromycin 800 milligrams once daily for 5 days is effective in the treatment of acute sinusitis and comparable to widely used standard comparators in this indication. Telithromycin also proved to be highly effective against the four main pathogens encountered in this indication, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus, but also emerging strains of Streptococcus pneumoniae.

In conclusion, telithromycin was consistently shown to be effective in 14 clinical efficacy studies in treatment of three respiratory tract indications: in acute exacerbation or acute sinusitis with a treatment duration of 5 days, which was equivalent to a 10-day treatment regimen of a standard antibiotic given two to three times daily, and will favor a better compliance; in community-acquired pneumonia with a treatment regimen of 7 to 10 days. And a large experience has been obtained in patients most likely to develop complications in all three

indications.

Finally, as mentioned earlier, one of the main differentiating features of telithromycin is its very focused, targeted spectrum to respiratory tract pathogens, and high efficacy was demonstrated against both common and atypical pathogens in this indication, as well as against Streptococcus pneumoniae resistant to penicillin G or to the macrolides.

I would like to thank you for your attention, and I will now turn it over to Dr. Bhargava who will present the key clinical pharmacology results obtained with telithromycin.

DR. BHARGAVA: Good morning. Today I'm pleased to present the clinical pharmacology characteristics of telithromycin which primarily address two key pharmacokinetic issues raised by the FDA: first, the variability in the pharmacokinetics of telithromycin, specifically in the multiple-impaired population, and second the drug-drug interaction potential of this drug.

To address these topics, we have extensively examined the pharmacokinetics of telithromycin, and I will cover three important aspects.

First, I will present the key plasma and tissue pharmacokinetic characteristics of telithromycin supporting the once-a-day dose regimen and high and sustained tissue

levels for the duration of the dosing interval.

Second, I will present the multiple elimination pathways of telithromycin which limits the increase of its exposure when elimination pathways are blocked.

And third, we will look at the drug interaction potential of telithromycin to impact levels of other drugs that are metabolized by the CYP3A4 pathway. Data will support that this effect is similar to that observed with widely used drugs such as clarithromycin.

The pharmacokinetic data shown on this slide has been confirmed in several other studies. In summary, a few important points about the plasma pharmacokinetics. Absorption is rapid, as shown by the short Tmax. Maximum plasma concentration of over 2 micrograms per ml are achieved. Steady state was rapidly achieved after the second or third dose with a terminal half-life of 7 to 10 hours.

Next, let's look at the tissue concentrations of telithromycin after a 800-milligram once daily dose to steady state. We see that in both tissues, the epithelial lining fluid as an example of extracellular tissue and alveolar macrophage for intracellular tissue, concentrations are rapidly achieved and maintained for 24 hours, the dosing interval. Note that levels in epithelial lining fluid, as high as 14.9 micrograms per ml were

achieved. Levels in the tissues are well above the targeted MICs.

There are multiple pathways of telithromycin elimination. As mentioned before by Dr. Jenkins, there is structural similarity of telithromycin to macrolides. I will present data to show that the disposition and exposure profile of telithromycin is similar to that seen with macrolides such as clarithromycin. The disposition profile shows that the absorption is good, over 90 percent, after oral absorption. 33 percent undergoes first-pass metabolism, resulting in an absolute bioavailability of about 60 percent.

Once in the systemic circulation, it has several routes of elimination. It can be excreted as unchanged drug in the feces with the biliary excretion or as unchanged drug in urine with a renal excretion, and it is further metabolized into several metabolites. Total metabolism is about 70 percent.

Three important points about the metabolism of telithromycin. One, about a third of the dose is mediated by non-cytochrome P450 which which are rarely associated with clinically relevant drug interactions. Another third is mediated by the CYP P450 isozyme. Data will shown that due to the limited involvement of the CYP3A4, the potential for increased exposure in situations when this pathway is

blocked is minimal. In addition, the well-known polymorphic isozyme 2D6 is not involved in the metabolism of telithromycin.

In collaboration with the FDA, we examined the exposure of telithromycin under conditions of impairment. The hepatic and renal study looked at the effect of mild, moderate, and severe impairment on telithromycin exposure compared with a healthy controlled population. The effects of 3A4 impairment were examined using a crossover design where telithromycin levels were measured in healthy subjects when they were either receiving or not receiving the potent 3A4 inhibitor ketoconazole.

Additionally, we stressed the system and looked at telithromycin exposure when both the metabolic and renal pathways were impaired. We did this by administering telithromycin to subjects who were greater than 60 years of age with renal impaired function and to whom we also administered ketoconazole to block their CYP3A4 pathway. A clarithromycin arm was also used in this study to compare the exposure seen with telithromycin in this population.

Let's examine the results from each of these studies.

First, the hepatic impairment study. The data in the mild, moderate, and severe groups were not different and hence are presented as combined data. In all stages of

renal impairment, there were no changes seen in either Cmax or AUC. Please note the increase in renal clearance for subjects with hepatic impairment compared to the sex- and age-matched healthy controls. These results indicate that renal elimination is a compensatory pathway in situations where the liver is impaired. These findings for telithromycin are similar to what has been well documented for clarithromycin.

Let us now look at the data related to renal impairment. The study compared a control group of subjects with greater than 80 mls per minute to subjects with different degrees of renal impairment, mild, moderate, and severe. The mild and moderate groups showed small increases in Cmax and AUC, and in the severe renal group, the increase was limited to 1.5-fold and 2-fold in Cmax and AUC, respectively.

Here we see the effects of blocking the CYP3A4 pathway by the administration of ketoconazole. We see that with a strong inhibitor, there is a 1.5-fold change in Cmax and about a 2-fold change in AUC. With other inhibitors such as itraconazole, a lesser interaction was observed, and with grapefruit juice no interaction was observed.

At the request of the agency, we looked at the additive effect on exposure when both the renal as well as the metabolic pathways were impaired. In these patients

with multiple impairment, the Cmax and AUC seen here are only modestly above those seen previously when only the CYP3A4 pathway alone was blocked. Thus, the added effect of renal impairment on top of the 3A4 pathway being impaired is minimal.

While the intent of the study was to recruit individuals whose creatinine clearance was between 30 and 80, we had two individuals in the telithromycin group who had creatinine clearance less than 30 mls per minute. Data for both these individuals is shown here, and higher exposures are seen as compared to those with creatinine clearance greater than 30 mls per minute. We will put these levels into perspective in a few moments.

As mentioned previously, a clarithromycin arm was used in this study to look at the exposure of this drug in a similar population. The Cmax and AUC of clarithromycin are shown here. Let's put these exposures seen for both drugs in the multiple impaired population in context.

These are the exposure data for telithromycin and clarithromycin that we have just seen in the multiple impaired population. Cmax data are shown on the left panel and AUC on the right panel. We now add the comparative healthy population for these two drugs. The healthy population for telithromycin is from an Aventis study, and

the healthy population for clarithromycin is from the literature. We can see that the increase in Cmax and AUC for telithromycin is comparable to that seen for clarithromycin in this population. These data demonstrate that in this population, where multiple pathways are blocked, the increase in exposure of telithromycin is limited and comparable to that observed with clarithromycin.

In addition, the electrocardiograms obtained in this study were analyzed for prolongation of the QT interval using well-defined outlier criteria. That is, QT corrected outlier criteria of QTc, that is, QT corrected for heart rate which is greater than 450 milliseconds for males and greater than 470 milliseconds for females or a change of greater than 60 milliseconds measured at multiple time points throughout the dosing interval following drug ingestion. These outlier criteria were not met by any subject in the telithromycin treated group during the entire dosing interval.

So let's summarize the data that we have just seen.

The data shown here are the fold increase in telithromycin exposure in special populations when compared to healthy controlled data. All data shown here are at the 800 milligram dose under steady state conditions. Two

important points from this slide.

First, we see that under various conditions of impairment, hepatic impairment, renal impairment with mild, moderate, or severe, CYP3A4 inhibition with a potent inhibitor ketoconazole and milder with itraconazole, and including in the multiple impaired population when creatinine clearance is greater than 30 mls per minute, the telithromycin levels, as measured by Cmax and AUC, show no significant increase in exposure. The only exception is the situation with multiple impairment where creatinine clearance is less than 30 mls per minute. A dose adjustment is recommended in this population.

Second, in studies where we had a control population as part of the same study, the variability estimates are shown. We see that the variability is limited and that the upper end is well defined.

In the last few slides, we have looked at the effect of impairment on telithromycin levels. We now change gears and look at the potential of telithromycin to impact the levels of drugs that are metabolized by the 3A4 route.

Simvastatin is a drug with high first pass effect and low bioavailability. Due to this, it is known to interact with several inhibitors of the CYP3A4 isozyme. When telithromycin and simvastatin are given together, we

see that there is an increase in both the levels of simvastatin and simvastatin acid.

To put this level of interaction in context, we see the effect of several other CYP3A4 inhibitors on the levels of simvastatin. We see that the interaction with clarithromycin is similar to that seen with telithromycin. And a larger interaction on simvastatin is seen with grapefruit juice and itraconazole.

Telithromycin is administered once a day, and knowing the kinetics of CYP3A4 inhibition, we conducted a study to evaluate the telithromycin-simvastatin interaction when the drugs are administered together or administered separately. The data showed that we see a more than 50 percent reduction in the level of interaction for both simvastatin and simvastatin acid under these dosing conditions.

Before we move on, I'd like to point out that as mentioned in the sponsor's briefing book, data analysis for the clarithromycin-simvastatin interaction shown on the previous slide and the telithromycin-simvastatin interaction shown on this slide have been recently completed and submitted to the agency.

As stated before, simvastatin is sensitive to the inhibition of 3A4. Two other 3A4 substrates were also investigated, midazolam and cisapride. Comparison of

interaction between telithromycin and clarithromycin on these 3A4 substrates are shown here. We see that the level of interaction for telithromycin is similar to that observed for clarithromycin for both of these 3A4 substrates. Thus, the CYP3A4 inhibition potential of telithromycin is similar to or less than that observed with clarithromycin.

In summary, telithromycin pharmacokinetics have been extensively investigated under stressed conditions. Its pharmacokinetics are reproducible and variability is limited.

Telithromycin rapidly achieved plasma and respiratory tissue concentrations above the MICs of the relevant pathogens.

Telithromycin has multiple pathways of elimination and its metabolism by the CYP3A4 isozyme is limited. It is also metabolized by non-CYP3A4 P450 pathways and these properties limit its potential for increased exposure when multiple pathways are blocked. The potential for telithromycin to increase the exposure of other drugs that are metabolized by the CYP3A4 pathway is comparable to clarithromycin and significantly less than potent inhibitors such as ketoconazole.

In addition, telithromycin is dosed once daily and for a limited duration in patients with respiratory

tract infections, further lessening the potential for drug interactions.

I thank you for your attention and would like to ask Dr. Lagarenne to present the safety data on telithromycin.

DR. LAGARENNE: Thank you and good morning.

Today I'm pleased to present our extensive safety experience with telithromycin with data available from three key sources.

Phase III studies enrolled nearly 4,500 telithromycin-treated subjects, with nearly 3,000 of these in controlled clinical trials.

Study 3014, our large usual care study, enrolled more than 24,000 patients, including more than 12,000 subjects treated with telithromycin, making this the largest randomized comparative clinical trial ever performed for an anti-infective agent. This unique study, designed in collaboration with the FDA to address concerns raised at the last advisory committee, utilized a variety of methods to increase exposure in more diverse risk populations and to enhance safety monitoring.

And finally, telithromycin has been approved and marketed in Europe and other countries for over 15 months, providing more than 1.5 million exposures to help us confirm the overall safety profile of telithromycin.

Phase III studies provided an initial assessment of the overall safety profile of telithromycin, and I will focus on the controlled clinical trials.

This slide displays the most frequent adverse events reported in phase III controlled clinical trials irrespective of investigator causality. The pooled comparators in these studies included penicillins, beta-lactams, macrolide, and quinolone antibiotics. The frequency of subjects with adverse events was balanced between treatment groups, with the most common adverse events reported in both treatment groups being gastrointestinal in nature.

In controlled phase III studies, adverse events leading to discontinuation of study treatment, serious adverse events, serious adverse events considered possibly related to study drug and deaths were all uncommon and balanced between the treatment groups.

The most common events leading to drug discontinuation were gastrointestinal in nature. Most of the serious events -- as you can see here, there are very few that were considered treatment related -- were infectious or respiratory events related to underlying illnesses rather than to the study drug, and none of the deaths in these studies were considered related to study drug by the investigator.

Blurred vision was an uncommon event of note that occurred more frequently in the telithromycin-treated subjects in phase III studies. However, the incidence was very low, occurring in 0.6 percent of telithromycin-treated subjects. Further, this event was generally mild, of limited duration, fully reversible, and with no sequelae. There were no serious reports and only one subject in controlled trials required discontinuation due to this event.

This visual effect was further characterized in two phase I studies and potential mechanisms were also investigated. Healthy volunteers were administered supratherapeutic doses of up to 2,400 milligrams and a number of ophthalmic examinations were performed. Blurred vision was most frequently described as a delay in focusing from near to far vision and occurred almost exclusively in subjects under the age of 50. Onset was generally within a few hours of dosing which corresponds to the Tmax observed in the clinical pharmacology studies, with rapid and full recovery noted within 2 to 3 hours. Although described as blurred vision, actual decreases in visual acuity were not noted. More importantly, thorough evaluation ruled out etiologies associated with potential irreversible vision loss such as angle closure-glaucoma and retinopathy. Altogether these findings suggest a mechanism consistent

with a slight delay in focusing.

Phase III studies also included detailed cardiac evaluation designed to determine the relevance of data obtained from preclinical studies revealing activity at the IKr channel comparable to those observed with currently marketed macrolide antibiotics. ECGs were performed pretherapy and on therapy in nearly 2,500 subjects. These ECGs revealed a minimal mean change of 1.5 milliseconds in QTc, that is, the QT corrected according to Bazett's formula for heart rate, with no differences noted in the rare QTc outliers such as on-therapy increases in QTc greater than 30 or 60 milliseconds or QTc's over 500 milliseconds, and this was versus both macrolide and non-macrolide comparators.

We know that noncardiac drugs with QT effects of concern, that this effect is generally a concentration-dependent effect. So we have performed an assessment of drug concentration and QT interval in subjects from the phase III studies.

As can be seen here, plasma drug levels were drawn 2 to 3 hours after drug administration and matched with QTc intervals that were obtained within an hour of the plasma sample. More than 1,500 matched data points were analyzed over a wide variety of concentrations. A linear best fit concentration versus QTc relationship revealed a

shallow slope of 0.88 milliseconds per microgram per milliliter. But more importantly, a very low correlation is manifested by the minute r squared value of .0025 which, translated in laymen's terms, essentially means that teli concentrations explained less than 3 one-thousandths of the QTc interval variability observed in these subjects.

Additionally, as noted by the data highlighted in the rectangle and in this box here on this slide, this observation is supported by the absence of any meaningful QTc increases in those patients with the highest plasma concentrations. For instance, we see here no QTc over 450 for men or 470 milliseconds for females.

In addition to the visual and cardiac evaluations, detailed hepatic evaluations were also included in the phase III studies. As seen here, ALT elevations greater than 3 times upper limit of normal were similar between treatment groups, as was the overall proportion of subjects experiencing hepatic events.

As noticed in the briefing document from the FDA and Aventis, our previous NDA submission reported a single case of clinical hepatitis. The subject in question had a preexisting, ill-defined baseline hepatic abnormality as evidenced by ALT values approximately 2 times the upper limit of normal. Plus, he had baseline eosinophilia, consistent with his underlying asthma condition. Four days

after completing a 10-day course of therapy for pneumonia, the patient experienced a gastroenteritis-like illness shared by several other family members. Six days following this, symptomatic transaminase elevations without hyperbilirubinemia were noted.

A liver biopsy during this episode has been reviewed by our pathology expert, Dr. Rubin, who is here today and who would like to review these slides later, if possible, during the Q&A. His review demonstrated focal accumulation of macrophages with moderate liver cell dropout. Eosinophils observed on biopsy were entirely consistent with the background eosinophilia due to asthma.

The patient recovered within 6 weeks with no further intervention.

Nine months later and with no further exposure to telithromycin, the patient experienced an asymptomatic increase in transaminase levels. A second liver biopsy exhibited chronic active lymphoplasmacytic infiltrate, some fibrosis and nodule formation suggesting early cirrhosis, consistent with progression of autoimmune hepatitis.

In view of the preexisting baseline ALT elevations noted before the first episode and in view of the second biopsy findings with the additional presence of positive autoantibody noted during that second episode, the initial biopsy retrospectively is consistent with an early

autoimmune hepatitis following a pattern of exacerbations and remissions.

Following the second episode, the patient has been followed closely with regular lab monitoring every 6 months for the past 4 years. ALT elevations have remained similar to his baseline values of approximately 2 times the upper limit of normal and the patient has been asymptomatic.

This case has been extensively reviewed and discussed with our hepatic expert consultants who are also here available today to discuss the case further if needed. However, as far as we are aware, there are no published case reports and no drugs known to induce an indolent, chronic hepatic injury following a single short course of therapy. Given these facts, a telithromycin-related etiology for this patient's underlying hepatic disorder appears highly unlikely. Nevertheless, we have conducted an extensive assessment of clinical hepatic events in our large usual care study and we have closely evaluated all post-marketing reports of hepatic events, as will be described shortly.

I will now focus on study 3014, our large comparative clinical endpoint study performed in a usual care setting and designed in collaboration with the FDA.

Permit me to outline the key features of this

trial which was designed specifically to address the concerns raised at the previous advisory committee by capturing major clinical outcomes in a usual care setting. Study 3014 was a randomized, open-label comparative study. More than 24,000 subjects were enrolled and treated with either telithromycin or amoxicillin-clavulanic acid. Several approaches were undertaken to enrich the population with potentially at-risk individuals and thereby enhance safety signal detection.

First, the study was performed with minimal exclusion criteria to simulate real-world experience. Specifically, we enrolled large numbers of patients who exhibited relevant comorbidities and who were taking a variety of concomitant medications.

Second, in response to the FDA's recommendations, we increased the treatment duration for acute exacerbation of chronic bronchitis from the 5-day course used in the phase III trials to 7- to 10-day course used in this study.

Third, enrollment targeted older subjects, and 46 percent of subjects in this study were age 50 or older.

And lastly, 40 percent of the subjects in this study had either community-acquired pneumonia or acute exacerbation of chronic bronchitis as opposed to the sinusitis indication.

Safety data collection was designed to capture prespecified adverse events of special interest, or AESIs, in the usual care setting. These AESIs consisted of cardiac, hepatic, visual, and vasculitic events. Office visits were planned at the pretherapy visit, that is, day 1, and at a post-therapy visit between days 17 and 22. Contact at a third late post-therapy visit either by phone or office visit was planned for days 30 to 35. However, it's once again important to note that all subjects with adverse events of special interest or serious adverse events were asked to return to the office for this late post-therapy assessment.

Additionally, it's also important to note that hepatic lab testing was systematically obtained at pre-therapy and the post-therapy visit. The investigators were instructed to review and report all adverse events occurring during the 35-day window of observation, focusing particularly on identifying all AESIs.

The four AESIs are defined on this slide. Hepatic AESIs included all reports of hepatitis, jaundice, or any worsening of a preexisting hepatic condition, but in addition, all cases of ALT greater than or equal to 3 times the upper limit of normal were systematically designated as AESIs whether symptomatic or not.

Cardiac AESIs included torsades de pointes or

other ventricular arrhythmias, syncope which was defined as a complete loss of consciousness, cardiac arrest, and all unwitnessed or unexplained deaths. Additionally any death occurring during the period of observation, that is, through day 35, was designed as a cardiac AESI.

Visual AESIs included all cases of blurred vision and associated complaints.

And lastly, vasculitic AESIs included purpura or other clinical signs of vasculitis.

Additionally, any other events so designated by the investigator were considered AESIs.

These definitions were intentionally defined very broadly to cast a wide net and screen for all potential clinical endpoint cases.

All adverse events -- that's not just AESIs, but rather all adverse events -- and all lab values were reviewed daily by the sponsor and the CRO to ensure complete identification, collection, and follow-up of all AESIs.

All AESIs were then investigated using detailed questionnaires designed to maximize and standardize the available information for each AESI. The questionnaire included such items as symptoms, diagnostic workup, information that might exclude other causes for the event, and details on the temporal relationship of the event to

study drug administration.

In addition, hepatic lab tests were systematically performed at the pre-therapy and post-therapy visits to ensure the capture of all potential hepatic endpoint cases. For all ALT levels greater than or equal to 3 times or more of the upper limit of normal, a specific algorithm was followed by obtaining an additional standardized lab evaluation which included total and direct bilirubin, serum transaminases, alkaline phosphatase, complete blood count with differential, prothrombin time, and hepatitis serologies. Any additional labs or diagnostic evaluations were to be obtained and reported per investigator clinical discretion.

Each AESI was to be followed to clinical resolution.

It is important to note that AESIs are not study endpoints in this study but instead represent potential endpoints. Rather, the blinded, independent expert clinical event committees, or CECs, were provided complete information packages for all AESIs as described above. These packages were then reviewed and adjudicated by the CEC to identify predefined clinical safety endpoints. Additional information was provided as requested by the CEC. The study endpoints will be presented shortly.

Follow-up was actively pursued in all subjects enrolled in this study. Only 2 telithromycin-treated subjects and 1 AMC subject were treated but had no post-baseline assessment. Thus, virtually all of the treated population had an assessment after starting study drug and constitute the safety-evaluable population.

99.5 percent of telithromycin subjects and 99.2 percent of AMC subjects had detailed adverse event information available on day 28 or later, that is, detailed AE status information. We obtained vital status, that is, additional information or other information whether the subject was alive or dead, in an additional 0.5 percent of subjects, resulting in an overall 99.8 percent out of these 24,000 subjects with follow-up information obtained at day 28 or later.

I will now review the study results.

The adverse event profile, including total subjects with adverse events, discontinuations due to adverse events, and serious adverse events, were similar and balanced between treatment groups. As noted in the phase III studies, gastrointestinal events were again the most commonly reported events in both treatment groups.

Discontinuation rates were low and comparable between treatment groups. As in phase III, the most common events leading to discontinuation were gastrointestinal in

nature.

Serious adverse events were also uncommon, occurring in approximately 1 percent of subjects, and again as noted in phase III, these serious events were primarily unrelated and due to underlying conditions.

As noted on this slide, the size of study 3014 allowed us to assess safety in significant numbers of subjects exhibiting comorbid conditions and taking a variety of concomitant medications of interest such as those metabolized by the cytochrome P450 system. The overall frequency of adverse events in these subgroups was balanced between treatment groups. Of particular note, 1,420 telithromycin-treated subjects were also taking HMG CoA reductase inhibitors metabolized by the CYP3A4 pathway, that is, simvastatin, atorvastatin, or lovastatin. However, no reports of rhabdomyolysis or significant myopathy were seen in any of these subjects.

I will now discuss the key analyses for this study.

Analysis of the hepatic AESIs revealed that they were uncommon and balanced between treatment groups occurring in approximately 1 percent of subjects. Most of these represented asymptomatic ALT elevations noted during the routine lab monitoring rather than clinically manifest illnesses. With the exception of 1 AMC subject who refused

to give any further clinical information to the investigator, all hepatic AESIs were followed to clinical and/or lab resolution. There were no reports of chronic or immune-mediated hepatic injury, and most importantly, there were no occurrences of drug-related hepatic failure, liver transplant, or death from primary hepatic causes in either treatment group in this study.

The predefined clinical hepatic endpoint in this study was possibly drug-related clinically significant hepatic injury. Predefined guidance for the adjudication of the hepatic endpoints included the presence of clinical signs or symptoms, a meaningful increase in ALT of at least 3 times the upper limit of normal, the exclusion of other common causes such as cholelithiasis or viral hepatitis, and the new onset of symptoms at day 5 or later so as to differentiate drug-related symptoms from those associated with the underlying infection. However, it's important to note that all final endpoint determinations were ultimately made according to the blinded CEC's expert clinical judgment and discretion.

Positively adjudicated endpoints, as can be seen here, were observed in 3 telithromycin and 2 AMC subjects with considerable overlap of the 95 percent confidence intervals. Of note, the five endpoints events were mild or moderate in intensity, and recovery was

documented in all cases but the 1 AMC subject who previously was mentioned and refused follow-up.

One endpoint subject had a liver biopsy performed during the study. This case has been reported in the FDA's and the sponsor's briefing documents and is discussed here. This telithromycin-treated subject with documented cholelithiasis demonstrated elevations in ALT, alkaline phosphatase, and bilirubin on day 23 following a 10-day treatment for pneumonia. There was no eosinophilia noted. Due to the cholestatic presentation and increasing alkaline phosphatase levels, the subject had an abdominal ultrasound performed on day 30 revealing cholelithiasis and thickening of the wall of the gallbladder. On day 36, the patient underwent laparascopic cholecystectomy. Gallbladder pathology was consistent with cholelithiasis and cholecystitis, and simultaneous liver biopsy supported this diagnosis with cholestasis, mild fibrosis, minimal inflammation, and no eosinophils noted. The patient fully recovered.

As mentioned previously, one of the main aims of the study was the detection of clinically evident drug-related hepatic adverse events. A review of hepatic lab measurements, performed primarily as part of our thorough case ascertainment in this study, is presented here, focusing on criteria that have been proposed to attempt to

predict untoward hepatic-related clinical outcomes.

This slide presents the frequency of noteworthy hepatic lab values for subjects with both normal and abnormal values at baseline. ALT elevations greater than or equal to 3 times the upper limit of normal were comparable and balanced between treatment groups, occurring in approximately 1 percent of subjects. The incidence of ALT elevations greater than 8 times the upper limit of normal, or approximately 250 units per liter, was uncommon but tended to be numerically higher in the telithromycin group. These events were predominantly asymptomatic lab abnormalities of a moderate level, in the range of 300 to 500 units per liter, that were reversible.

Recently greater emphasis has been placed on assessing combined elevations of ALT and bilirubin. Here we see the combined elevations of ALT greater than or equal to 3 times the upper limit of normal with a bilirubin greater than or equal to 1.5 times the upper limit of normal were also uncommon but, on the other hand, tended to be more frequent in the AMC group.

And lastly, 1 patient in the AMC group exhibited a pattern of elevated ALT with clinical jaundice, that is, a bilirubin greater than or equal to 3 milligrams per deciliter, and I believe this patient's bilirubin was close to the 5.1 or 5.2 level and with no elevation in

alkaline phosphatase. And this was also considered a clinical endpoint.

This sort of value here is considered the most, perhaps, interesting of these lab analytes because according to the famous or infamous Hy's Rule, patients who exhibit these kinds of findings have a greater tendency to have significant sequelae to their hepatic event. However, it should be noted that all of these patients recovered and there were no similar cases of hepatocellular jaundice seen with telithromycin.

Overall, when looking at these different analyses, it's important to remember that the sensitivity, specificity, and predictive value of these have not been firmly established and remain largely unknown.

I would now like to focus on the second AESI, cardiac events. The focus of this investigation was clinical cardiac events reflecting possible ventricular arrhythmic events. ECGs were obtained only as needed according to the investigator's clinical judgment. Cardiac AESIs were uncommon and balanced between treatment groups, occurring in 0.3 percent of subjects in both treatment groups. As mentioned previously, all deaths occurring up to day 35 were considered cardiac AESIs. These deaths were also similar and balanced between treatment groups, and none of these deaths were considered treatment-related as

assessed by the investigator.

The cardiac CEC also performed a blinded review of all deaths to determine those that were presumed arrhythmic in origin. Please note that all cases identified in the telithromycin group occurred 7 days or later after study treatment, thereby mitigating against any causal relationship.

This slide presents the cardiac AESIs noted for the large number of subjects enrolled in study 3014 with important baseline cardiac risk factors. Enrollment of these at-risk subjects and more importantly the proportion of these subjects experiencing cardiac AESIs was balanced between treatment groups. I think these numbers are also a little bit unprecedented in terms of phase III studies in terms of just the numbers of patients that you see here in these groups.

The cardiac endpoint in study 3014 was any event likely to represent malignant ventricular arrhythmia and that had a reasonable temporal relationship to study drug administration. No cardiac endpoint was identified for telithromycin. A single cardiac endpoint, sudden death in a subject treated with amoxicillin-clavulanic acid, was identified by the CEC. Thus, the CEC identified no increased risk for malignant ventricular arrhythmic events for telithromycin in this study.

Next I would like to focus on the third AESI in this study, visual events. The visual endpoint was drug-related blurred vision. Positively adjudicated endpoints were identified in 0.6 percent of telithromycin subjects and 0.4 percent of AMC subjects. Overall, the characteristics of this event were similar to those seen in phase I and phase III, with the reported median onset within 1 hour after dosing, with a median duration of 2 hours, and the majority of cases were of mild to moderate intensity with infrequent severe blurred vision reported in only .04 percent of telithromycin-treated subjects.

Discontinuation of therapy due to blurred vision was uncommon, noted in 0.2 percent of telithromycin subjects, and some impact on activity occurred in approximately 0.3 percent of teli subjects, most frequently described as difficulty reading.

It should be noted that no telithromycin subject with blurred vision reported any accidental injury and, moreover, that all of these cases were fully reversible.

Finally, before moving to the next slide, I would like to mention that for the fourth AESI, vasculitic events, only four combined AESIs were identified in the entire study with three reported for telithromycin and one for AMC. However, there were no positively adjudicated

endpoints of drug-related vasculitis in either treatment group.

I would now like to address the extensive post-marketing experience that we have accumulated with telithromycin thus far. These data help us confirm product safety in a real-world setting and also to assess the clinical relevance of any unanswered safety concerns remaining from earlier experience.

Telithromycin is marketed in many countries, including Germany, France, Belgium, Italy, Spain, Mexico, and Brazil, and over 1.5 million courses of therapy have been administered since marketing began in October of 2001 with France and Germany accounting for nearly 1 million exposures. It should be noted that both of these countries have well developed and sophisticated post-marketing safety surveillance and reporting systems.

Of note, our marketing data indicates that approximately 10 percent of prescriptions represent re-exposure, which adds a useful new dimension for safety assessment that's generally absent from phase III studies. In addition, Aventis has intensively followed up adverse event reports and has utilized standardized questionnaires to guide follow-up on reports of adverse events of special interest. To date, the post-marketing safety profile of telithromycin confirms the safety profile seen in clinical

trials, with no new or unexpected safety signals identified.

This post-marketing review that I will present includes updated data through the end of December 2002. As seen in the clinical trials, the most commonly reported adverse events were gastrointestinal in nature, with dizziness, headache, and blurred vision also noted. Therefore, I will focus the post-marketing review on the visual, cardiac, and hepatic AESIs discussed in detail in study 3014.

The majority of visual events seen in post-marketing reports are similar in character to those identified in the clinical trials. As in clinical trials, most commonly reported events remain blurred vision, abnormal focusing, and visual abnormality. 78 percent of these events occurred in patients less than 50 years of age, again consistent with an effect on focusing. The visual events are generally of limited duration, with full recovery noted.

While specifically noted in the FDA briefing package, although isolated reports of "loss of vision" have been received, in each instance where follow-up has been completed -- and this represents actually the majority of these reports -- they have, in fact, revealed varying degrees of blurred vision and not true vision loss.

Most importantly, no evidence of sequelae was noted in any case report, and to date we have received no reports of accidental injury in patients either with or without blurred vision after more than 1.5 million exposures for telithromycin.

With respect to cardiac events, post-marketing findings are again consistent with the experience in the clinical trials setting. There have been no reports of sudden or unexplained deaths and no confirmed cases of torsades de pointes. Two questionable reports have been received.

The first case reported as a torsades de pointes was a report demonstrating fatal ventricular fibrillation but with a QT interval noted to be normal less than 30 minutes prior to the fatal arrhythmia. Polymorphic ventricular tachycardia characteristic of torsades was not identified upon expert review of this case. Moreover, this subject had multiple risk factors for sudden death and began having syncopal episodes 3 days prior to administration of telithromycin. For these reasons, we do not believe that this case represents either torsades de pointes or a drug-related event.

For the second report, a complete and thorough follow-up investigation failed to identify an actual patient or event. The original reporter did not treat the

patient for the event but initially reported a specific physician and hospital where the event allegedly occurred. However, the specified physician was contacted at the hospital and denied any knowledge of such patient, and following an extensive search of the hospital emergency and cardiac units, including all possible related services on or around the specified dates, he in fact determined that no patient had been treated for the same or similar diagnosis.

Additionally, it's interesting to note that there have been no other reports of any ventricular arrhythmias from post-marketing surveillance. Thus, we believe that the available post-marketing data in over 1.5 million patients exposed worldwide support no increase for cardiac risk associated with telithromycin therapy.

With respect to post-marketing hepatic adverse events, reports were uncommon, with 64 events reported in 28 patients. No reports of drug-related hepatocellular jaundice have been received. There have been four reports of cholestatic jaundice received. However, one of these patients had a well-documented acute mononucleosis, and all of these patients recovered fully.

There have also been no reports of chronic or immune-mediated hepatic injury received from the post-marketing experience.

Additionally, there have been no reports of drug-related hepatic failure, liver transplant or death. We have received recently a single report of a fatal acute hepatitis A with hepatic failure in an elderly gentleman with a documented hard nodular liver and who has undergone expert review with our consultants. This report is not considered drug-related by either our experts or the reporting physician.

This 75-year-old patient experienced serum transaminase and bilirubin increases and marginal alkaline phosphatase elevation 1 day after completing a 5-day course of telithromycin for a febrile illness diagnosed as acute exacerbation of chronic bronchitis. The patient also had received doses in excess of 4 grams per day of acetaminophen for 4 to 5 days prior to the event. One day after admission, the patient underwent emergency laparotomy due to worsening clinical status presumed secondary to acute cholecystitis, as suggested by the physical examination and abdominal ultrasound, but this was not confirmed on surgery. However, during the laparotomy, a hard nodular liver was noted, strongly suggestive of significant preexisting chronic hepatic disorder. Liver biopsy was not performed due to bleeding complications during the surgery.

Lab evaluation, which had been initiated on

admission and returned 1 day following the surgery, revealed documented acute hepatitis A with unequivocal high elevated IgM antibody and additional documentation of a recent acute Q fever. The patient experienced post-surgical complications, including disseminated intravascular coagulation and multi-organ failure and died on day 11.

This patient's clinical course is consistent with an underlying chronic hepatic disorder as evidenced by the hard nodular liver noted at surgery with superimposed acute hepatitis A, a well-documented cause of acute liver failure.

Additionally, we have reviewed this case in the context of FDA Freedom of Information post-marketing surveillance data and determined that the occurrence of one such case in over 1.5 million exposures in an infectious disease population is consistent with the background rate noted with other marketed antibiotics.

In summary, extensive experience with telithromycin in diverse populations and high risk subgroups has demonstrated the safety of telithromycin. This experience includes more than 16,000 subjects treated with telithromycin in phase III clinical trials and more than 1.5 million exposures in the post-marketing setting.

Overall, telithromycin has displayed a safety

profile comparable to marketed antibiotics. It is well tolerated with the most commonly reported adverse events in the gastrointestinal system and with low rates of discontinuation of therapy.

Blurred vision was uncommon, generally mild to moderate in intensity, of limited duration. The mechanism appears consistent with a delay in focusing as supported by the age distribution of the event and the symptom description. Importantly, detailed ophthalmic examinations in phase I have excluded potentially serious or irreversible etiologies, and both clinical trial and post-marketing reports have revealed no sequelae or associated injuries.

An extensive cardiac evaluation has also been performed with telithromycin. No increase in ventricular arrhythmic events or cardiac deaths was noted in the phase III studies or the 24,000-subject usual care study 3014. Notably, these combined studies enrolled significant numbers of older subjects, subjects with significant cardiovascular disease, and subjects taking a variety of concomitant antiarrhythmic drugs and drugs with known potential to prolonged QT interval. Similarly, the post-marketing experience reveals no evidence of excess risk and no confirmed cases of torsades de pointes after more than 1.5 million exposures.

And lastly, following extensive hepatic evaluation, no hepatic safety signal has been confirmed. Clinical hepatic events occurred at rates comparable to currently marketed antibiotics in both study 3014 and in the post-marketing arena. Moreover, there have been no cases of drug-induced hepatocellular jaundice, no cases of chronic or immune-mediated hepatic injury, and no cases of drug-related hepatic failure, liver transplant, or hepatic deaths observed.

Thus, telithromycin's safety profile has been carefully evaluated and demonstrated in over 16,000 clinical trial patients and over 1.5 million patients treated in the real-world setting.

I would now like to call upon Dr. Iannini to put this large clinical experience into perspective and to present the final conclusions. Thank you.

DR. IANNINI: In brief summary, optimal therapy for community-acquired respiratory tract infections requires that all likely pathogens be well covered by an agent with a targeted spectrum that includes both common and atypical pathogens.

The rate of resistance of respiratory pathogens to commonly used therapeutic agents is currently high and increasing and may shorten their useful life.

Current antimicrobial agents have limitations

that result in an unmet medical need. Beta-lactam antibiotics are limited by poor activity against atypical organisms, penicillin-resistant pneumococci, and in some cases beta-lactamase positive Haemophilus influenzae.

The macrolides are limited by appreciable pneumococcal resistance.

And fluoroquinolones have a broad spectrum that is not targeted to respiratory pathogens. Resistance development to fluoroquinolones by enteric and other Gram-negative rods is a clinical concern. Additionally, fluoroquinolone resistance mutations are present in Streptococcus pneumoniae and may limit the use of older agents in this drug class.

Telithromycin is as highly effective as comparators in the treatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis. It has the additional benefits of having a second site of ribosomal binding, concentration-dependent rapid killing, a targeted spectrum of activity that's well-suited for respiratory tract infections, and is active against resistant strains of Streptococcus pneumoniae.

Telithromycin is effective when given for short treatment durations, a feature that may promote better patient compliance and limits exposure time for drug-drug interactions.

Telithromycin has been shown to be a safe drug.

In addition to the phase III data presented here today, more than 1.5 million patients have been treated with telithromycin since its approval in European countries. No toxicity signals have emerged. Telithromycin's safety profile is comparable to widely prescribed antimicrobial agents even in a large 24,000-patient trial in usual usage situations.

The most common intolerances are gastrointestinal and most are mild to moderate. Visual events are uncommon, mild, and reversible with no sequelae. There's no evidence of increased cardiac risk when compared to other agents. No increased risk of clinically appreciable hepatic injury has been detected. Drug-drug interactions are limited because of multiple routes of elimination and short exposure times. Specific drug-drug interactions related to cytochrome P450 isoenzymes have been studied in detail and no major issues have been identified.

Telithromycin fulfills an unmet medical need for reliable empiric therapy for community-acquired respiratory tract infections. It brings the additional benefits of a second site of ribosomal binding, concentration-dependent and rapid killing, a targeted spectrum of activity unaffected by current common

resistance mechanisms, and requires short durations of treatment.

Telithromycin has a comparable safety profile to other marketed antimicrobial agents.

In conclusion, telithromycin would be a valuable option for clinicians and patients in the treatment of community-acquired respiratory tract infections.

That concludes our presentation. On behalf of the sponsor, I'd like to thank you all for your attention.

DR. LEGGETT: I think what we should probably do now is address some questions about this part of the study so that then we can all take a short break. We're running behind. So why don't we address questions to all the presenters from Aventis at this point. Don.

DR. PORETZ: Yes. I'd like to ask a question about Staph. aureus. You presented data on sinusitis, and I think there were 15 or 17 patients who had Staph. aureus sinusitis and they were all cured. But then you also presented data with the MICs on Staph. aureus, some of which were quite high. There were no patients, as I could tell, who had Staph. aureus pneumonia or acute exacerbations of chronic bronchitis due to Staph. aureus. I'd just like to know some more information about Staph. aureus and telithromycin and how telithromycin compares

with macrolides against Staph. aureus.

DR. LEROY: I will first answer the question regarding Staphylococcus aureus and sinusitis. First, we applied the rule of 10 to the 4th to qualify the patient with a Staphylococcus aureus. They were all susceptible to telithromycin in the acute sinusitis indication and just very few patients were erythromycin-resistant but susceptible to telithromycin, which we can see in non-constitutive strains.

But your question was larger and asked also about the overall efficacy of telithromycin. So I'll ask Dr. Jenkins, our microbiologist, to answer the question.

DR. JENKINS: Telithromycin is interesting in that it is very active against strains of Staph. aureus that have an inducible mechanism of resistance. In other words, they have inducible methylation of the ribosome. Those strains that have a constitutive production of the methylase enzyme, telithromycin is typically inactive.

And if you take a look at strains of staph that are either susceptible or resistant to methicillin, most of the methicillin-susceptible strains either are macrolide-susceptible in general or they have the inducible methylation mechanism. By comparison, the methicillin-resistant strains are almost uniformly constitutively producing the methylase enzyme.

DR. LEGGETT: Dr. Elashoff?

DR. ELASHOFF: Yes. I have three related questions. One is with respect to slide 34 in which you compare clinical cure by pathogen, but the comparator sample sizes seem to be very much smaller than the others. You didn't do those for most of the comparators, or it's simply not reported here, or what? That's question one.

DR. LEROY: The answer is that the telithromycin group includes the non-comparative trials which were meant to gather a lot of Streptococcus pneumoniae strains, and therefore we've gathered all information concerning telithromycin in comparative and non-comparative trials in this table.

DR. ELASHOFF: Okay.

The second question has to do with slides 37 and 38 which show clinical cure for resistant isolates for telithromycin, but don't show that same information for comparators. Presumably there are some cases that could be shown for comparators.

DR. LEROY: There were only a few cases because most of the experience was obtained in non-comparative studies for Streptococcus pneumoniae resistant for two reasons. One is that it's difficult to use a comparator which is not active on S. pneumoniae when there is a high rate of resistance. Ethics committees generally discard

those drugs as potential drugs to be used in a double-blind trial, and that clearly causes a real problem. Therefore, we would need to go to countries with lower rates of resistance, and in this case the number of strains isolated in the comparator group is small.

I will summarize that the most experience that we have is with clarithromycin, and I will show you two things. First, 4 or 5 cases of erythromycin resistance were cured with telithromycin, but 1 of the 4 had a late relapse. So in fact 3 out of 5 cases were cured with clarithromycin.

But I would like to show you the failure cases observed with telithromycin. It's the patients for the 4003 study. Slide on.

So that's an interesting case because it relates to the former presentation. There is a 51-year-old female with a Fine score which is not elevated, Fine score 2. Chest x-ray shows pneumonia. Pneumococcus shows a strain with a genotype ermB, and an MIC of 64 in the blood as well as in the sputum. And these strains were susceptible to telithromycin, but resistant to clarithromycin. Additionally, these patients had Moraxella catarrhalis isolated from the sputum.

On day 6, this pneumonia worsened with development of aseptic arthritis, and this S. pneumoniae

was isolated from the pus of the septic arthritis. Chest x-ray was unchanged. The patient was switched to an IV antibiotic and the patient was secondarily cured with several IV antibiotic use subsequently adjusting to the results obtained in this patient in the pus of the septic arthritis of this patient.

So despite the fact that we cannot study on a large scale efficacy in comparators to a patient, this is very informative of what exactly is the fear described by Dr. Iannini when taking care of such patients with possibility of resistant strains.

DR. ELASHOFF: And the third question is since apparently the strain wasn't determined in most of the cases in the comparative trials and if clarithromycin has a 31 percent resistance rate, you would expect in comparisons like slide 33 that clarithromycin might look a little worse than telithromycin if resistance is an important factor. And in fact, that doesn't seem to be the case.

DR. LEROY: We did not observe a rate of 30 percent in those pneumonia studies. They were performed, as Dr. Jenkins explained. The development started 5 years ago, so the recent trend overall in the pneumonia studies was around 10 percent. That does not allow us to show, in a study design for equivalence, any superiority. We would require a much larger number of patients, in the range of

the thousands, 2,000 or 3,000, per treatment group, to show that versus the same comparator.

DR. LEGGETT: Dr. Rupp.

DR. RUPP: Yes, just a few questions. In follow-up to the first question with regard to Staph. aureus, one of the failures in your community-acquired pneumonia trial was a patient who developed a Staph. aureus superinfection. Can you elaborate on any details on that? Where was the site and what was the susceptibility of that Staph. aureus isolate?

DR. LEROY: The site was urine in fact, which is uncommon. But it was the reason why the patient was treated with an additional antibiotic.

And the susceptibility. If I can have this patient. I have a loss of memory here. I'll get back to you with the susceptibility for this patient. But telithromycin is not meant to treat Staphylococcus aureus in urine in any case.

DR. LEGGETT: And if you have difficulty finding slides, we can address that after lunch to move this along.

Dr. O'Fallon.

DR. O'FALLON: I also had a question about the numbers, but before I say that, I would like to say I was very impressed by the number of studies you managed to get

done in that period of time. It was impressive to me.

But I did have a problem with the numbers, and this comes from your original packet when I was looking at that before we came into the meeting. And in your original packet on page 71, I notice this in all the studies. Basically there's an interesting differential in the loss of patients that were in your studies, and I wondered why this happened.

Table 6-5 in CAP, which would be a big one. It showed that, for example, in the per-protocol group, 84 percent of the telithromycin were there to be analyzed but only 77 percent of the comparators. And when we got down to the biological -- well, BMITT -- there were 46 percent of the telithromycin but only 35 percent of the comparators. And I was wondering why there was this differential loss. I saw that in all the studies, but this is the earliest one. Can you explain why you seemed to lose more from the comparators than from the telithromycin?

DR. LEROY: You're saying that the number of patients lost in the telithromycin group -- the test of cure or --

DR. O'FALLON: No, no. The telithromycin, you were doing a good job. Why were you losing them in the comparators? Because remember, you are comparing, so this would affect the comparisons to my way of thinking.

DR. LEROY: I understand your question. I'm not sure I have the precise table to look at. Are you speaking of the table where we pooled non-comparative and comparative, or are you speaking of a table where comparative trials were presented at the same time? Because that may explain the difference.

DR. O'FALLON: Well, it uses randomized. I didn't go through and check that out, but the first line on this is randomized. So I assume it's not the pre-marketing or anything like that. Post-marketing I mean or the enrichment studies. It says randomized, not registered, but randomized. Now, maybe it was a mistake. Maybe that's misleading, but if it's indeed the randomized, then --

DR. ALEXANDER: If I may. The particular --

DR. LEROY: I'm sorry.

DR. ALEXANDER: I'm sorry. The particular table that you are looking at does include patients from comparator trials as well as from open-label studies.

DR. O'FALLON: Okay.

DR. LEROY: It may have explained this difference in this case.

DR. O'FALLON: Okay, thank you.

DR. LEGGETT: Dr. Maxwell.

DR. MAXWELL: I have three quick questions. On slide 31, when you're looking at the community-acquired

pneumonia phase III studies, the western studies, of the 881 treated with telithromycin, what's the racial diversity? Do you have that data?

DR. LEROY: The ratio?

DR. MAXWELL: Racial diversity.

DR. LEROY: Racial diversity?

DR. MAXWELL: Yes.

DR. LEROY: We have these data in the briefing document, but I would say generally caucasian would be 82. I'll get back with a more precise -- but 82. Black would be 12 to 15 and Asian would be less than 5 percent. It would be an overall ball park. I can come back. I have it here. Slide on. So it was just lower for caucasian and approximately that, yes. And other includes in fact Hispanic.

DR. MAXWELL: My second question was looking at slides 58, 59, and 68, just in summary, I just wondered if there was any comparator or comparing to protease inhibitors or nucleoside, reverse transcriptase inhibitors, or if any of that was done but not reported just for my knowledge.

DR. LEROY: No, it was not done. Ketoconazole was thought to be the highest blocker, and therefore we did not repeat with a protease inhibitor.

DR. MAXWELL: Okay.

And my last question has to do with slides 97 and 100 looking at the visual adverse events or potential. I know that in study 1059 the plasma concentration of telithromycin was slightly higher in older patients and was slightly lower in the tears. And I couldn't understand why that would be. Yet, in study 1064 where you looked at 24 healthy subjects, you looked at the plasma concentration and reported that data, but there was no data about the concentration of the drug in tears. And I just wondered what that was, if you had that data.

DR. LEROY: I will ask the person who conducted the trial to help me with this question. Dr. Vashrom and Dr. Harding. Professor Harding was the investigator of the 1064, and I will ask Professor Vashrom also about the concentration seen in the tears.

DR. HARDING: The measurements in tears were not made on the 1064 study, only on the 1059. The subjects were undergoing a fairly rigorous program which involved 2 hours of visual testing, so there's a limit to what could be done.

DR. MAXWELL: Thank you.

DR. LEGGETT: Dr. Patterson.

DR. PATTERSON: I had a question also. I guess these are for Dr. Lagarenne regarding slides 97 and 100. In the study 3014, the rate of visual effects was noted to

be .6 percent. And was there a difference in the rate between women and men, and if so, what was the difference?

DR. LEROY: Yes, Dr. Lagarenne.

DR. LAGARENNE: The effect was seen a little bit more frequently in females, I think approximately 60 percent of the reports being in females.

DR. PATTERSON: And then on slide 100 in the post-marketing experience, you mentioned that the visual effects were of limited duration. I just wondered if you could be a little more specific about that. Was it hours, days?

DR. LAGARENNE: In post-marketing, it's hard to pinpoint because it's not a trial situation. It's patients often reporting to their physicians afterwards.

DR. PATTERSON: Or in the other studies, if you could comment.

DR. LAGARENNE: In the studies it was very consistent that generally it would occur within a few hours of dosing and would resolve generally within 2 to 3 hours, I would say, on average. There were some outliers outside of that, but for the most part it was consistent.

In the post-marketing, where we have specific information, I would say it ranges sometimes up to a day, sometimes 12 hours. It's hard to get a pinpointed number.

DR. PATTERSON: Thank you.

DR. LEGGETT: Dr. Wald.

DR. WALD: Could I ask for them to clarify exactly how was the surveillance done in the post-marketing patients? What was the mechanism by which adverse events were reported? Was it passive reporting? Was there some active mechanism?

DR. LAGARENNE: This is passive spontaneous reporting from each country. Germany and France being the two countries where most of our exposure has been have very developed pharmacovigilance reporting systems, and typically the reporting rates there are comparable to what you would see in the United States.

DR. WALD: And a follow-up question maybe someone from FDA could answer. How many doses of trovafloxacin were administered before the hepatotoxicity was observed?

DR. GOLDBERGER: It varied considerably, but I believe there were cases that were as few as just a couple of doses.

DR. WALD: I'm asking the total volume of --

DR. LEGGETT: How many millions.

DR. GOLDBERGER: Before hepatotoxicity.

DR. WALD: We're talking about a million-and-a-half patients now.

DR. GOLDBERGER: We started to see some

definite cases I think around the time that there were a million or so patients who had been exposed to product. There was some lag in terms of when events occurred and when they were reported, but I seem to recall we had at least one case, if not more, within a couple months after exposure, but that was so confounded, it's hard to understand really what happened. But in terms of starting to get a definite signal, there were at least a million exposures, and by the time regulatory action was taken, as I recall, it probably was closer to double that.

DR. WALD: And then a question about the number of patients who underwent sinus aspiration and the number that had a positive culture.

DR. LEGGETT: Did you understand? In your sinus studies, how many were positive out of the denominator of punctures?

DR. LEROY: Around 50 percent. We had two studies. One was higher than the other, but it was in the ball park of 50 percent of patients.

DR. WALD: And then the last question I'd like to ask is Haemophilus influenzae is about 200 times less susceptible than S. pneumoniae to this drug. And I understand that the endothelial lining fluid has a high concentration of macrophages. What would be the suspected fluid that would have sufficient antimicrobial activity in

patients with sinusitis? I think about sinus fluid levels, and then I'd ask the question were there any sinus fluid measured levels of telithromycin measured because I imagine that the level in the sinus fluid is yet less than the serum level.

DR. LEROY: There has been a study performed, which has not been submitted because it was completed recently. It was performed in France. The peak concentration in sinus tissue is around 6 micrograms per gram of tissue.

What we have also, which could answer partially your question, is that in the development that we're conducting in pediatrics, we see that the diffusion in middle ear fluid shows some degree of accumulation in this closed environment, and it's very consistent with this level of approximately 6. But it is still a related answer. It's not exactly a sinus fluid level.

DR. LEGGETT: Dr. Elashoff.

DR. ELASHOFF: For slides 33, 42, and 47, I would like to see the average or the distribution of the day on which the test of cure was made since there is a several-day window and I want to be assured that the days on which that happens are comparable for the drug and for the comparators.

DR. LEROY: For this question, we'll need to

get back to you. It requires manipulation.

DR. LEGGETT: Yes, thank you.

Dr. Cross.

DR. CROSS: With regard to slide 47, I was struck by the fact that the three studies reported, while each comparator and telithromycin are in the same ball park, there's quite a striking difference in terms of the efficacy, going from 91 percent in one study down to 75 percent in the other. And this is quite different from the similar slides on 42 and 33 for CAP and chronic bronchitis.

So my question is, was there any difference in terms of the endpoints or clinical design of these three studies which would explain the rather large inter-study difference? For example, was there a difference in the aspirations which were used as endpoints or any other differences to account for this?

DR. LEROY: No, there was no difference in design in all three studies. Slight differences in the patient population enrolled because when you perform a sinus puncture, generally it drives to a certain type of investigator, and the types of patients enrolled are slightly different. In addition, some ethics committees, for example, would not accept sinus puncture, in terms of mucosal thickening only, and therefore, one of the studies, the one with the highest cure rate, in fact, was done with

only air fluid level or total opacity in order to increase the yield.

One way to answer your question is to say we've looked at everything, any kind of factor that could explain the difference between the results in those studies, and the only thing that we've seen is that possibly in the 3005 study we have -- it was in a broader type of investigation, and there were more mucosal thickening only patients and sort of acute exacerbation of a subchronic state.

One important point here is that compared to the trial that you are seeing several years ago, the test of cure now is at 17 to 21 days. So, in fact, the results that you are seeing at over 85 percent, which were all often at the end of treatment, in these types of studies are more likely to be in the upper 70's or 80. Clearly when it was bacteremic -- that's why I showed this slide on the patients with the bacteremia, the sinus culture positive with the bacteria -- the cure rates were higher.

DR. LEGGETT: Dr. Lee.

DR. LEE: Yes. I have two questions.

First, could the sponsor address study 3009? There was a patient here on page 171, a 36-year-old woman with HIV who died rapidly after a course of therapy. Obviously, there are other complicating issues here, but I just wondered, first of all, do you have any more

information on that case, and second, what's the experience, just anecdotally, in patients who might be HIV-positive? Would there be any likelihood to think there would be an interaction with the heart drugs?

DR. LEROY: For this patient, first concerning the liver abnormalities, they were higher at entry than they were during the course of the study. So this patient came with a level of 2,000 transaminase at entry and was really a sick person.

The difficulty that we have is that we cannot perform HIV serology at entry and screen those patients. This is very legitimate. So sometimes in studies we have patients that have, in fact, a high degree of immunodepression that we cannot identify at the start of the study. And this patient had, in fact, an advanced HIV status that should have been treated with an antibiotic given intravenously, obviously.

DR. LEE: Sure.

DR. LEROY: And regarding your question about HIV patients, we have a very small experience in 3014 where we asked patients that were known to be HIV-positive. We didn't show any striking difference versus Augmentin. So it's very little experience in fact.

DR. LEE: So the first patient did have preexisting very high enzyme levels before receiving the

drug.

DR. LEROY: Yes, absolutely.

DR. LEE: The second question was on your post-marketing experience, they said there were four cholestatic cases, and we didn't hear any detail. Do you have more details on the four cases of so-called cholestatic hepatitis in the post-marketing experience?

DR. LEROY: Yes. We can review those details. I will ask Dr. Lewis to review those cases. He reviewed the cases and he'll be able to speak to it.

DR. LEWIS: Good morning. Jim Lewis from Georgetown University.

Actually I don't want to steal too much thunder from the FDA's presentation. They have this in their packet as well, and I think they were going to go over some of these cases. They selected five that were of significant interest.

One you've already heard about which was the French case which was hepatocellular with acute hepatitis A in a patient who probably had cirrhosis and was elderly.

The other cases that we have are from Germany that were cholestatic, and just briefly, one was a 61-year-old woman with underlying endocarditis who was treated. We have it up on the board. You can read the description. There were no liver enzyme values actually provided in this

case, but she did have a biopsy which is shown there. And this is the description from the reporting physician: focal fatty degeneration with moderate intrahepatic cholestasis, mild infiltrates, no eosinophils. And it was interpreted in their parlance as nutritive toxic origin, and it was included as a possible relation to telithromycin, but the reporting physician did not feel that it was actually suggestive of drug injury. It was sort of a nonspecific biopsy showing some cholestasis, and the patient recovered. But there's not any additional information provided with this one. So as with many other post-marketing reports, it's quite difficult to interpret completely.

The second case is a 70-year-old man from Germany with an underlying COPD, and you can read the rest of his history. A past history of hepatitis A, on several medications including steroids, treated for bronchitis. The enzyme pattern that was found here on the next slide, he's admitted on day 50, which is many days after the telithromycin was done, with, quote/unquote, a cholestatic hepatitis and jaundice. Again, we would probably not consider this cholestatic. This would be hepatocellular. Bilirubin went as high as 25 milligrams.

But the most important part of this history, which was left out in the materials provided by the FDA,

was that this man, after he had received telithromycin because of failure of that drug apparently to work, received a course of Augmentin. He had that for a couple of weeks we believe and it's well within the time frame when he's readmitted with this jaundice episode and a biopsy is done and is consistent with cholestatic hepatitis. So that's one case which is probably not related to the drug at all, and it would be much more likely to relate that to the course of Augmentin that he had.

The next case is a 33-year-old woman from Germany. Again, no significant history. She's on birth control pills for 3 years. Two days after she starts telithromycin, which she took for just a few days, for sinusitis and bronchitis, a 5-day course, she develops symptoms of abdominal pain, nausea, vomiting, fever, sweats, a form of collapse of some type. And her enzymes, again not cholestatic per se. These were mostly hepatocellular. Her ALT peaks at 823. Her bilirubin level is never appreciably high. There's no eosinophilia. There are no pretreatment values to look at in comparison. This happened just right after she started telithromycin.

So this one is listed as hepatocellular in nature, possibly related, but again it's an unusual presentation of drug injury. It doesn't really conform

very well to several other cases that are in the data set which are often asymptomatic and delayed after the drug has been received for several days. So this one again is -- who knows. It can be called possibly related. There was no biopsy here and no additional information. She recovered, as did the majority of these patients.

And then the final one which is in fact cholestatic. A 44-year-old woman again from Germany presented 2 to 3 days after she starts a 1-week course of therapy with tiredness and right upper quadrant pain. It was originally reported she may have been jaundiced, but that was later retracted. In fact, her bilirubin was never elevated. It was always normal. She had an alkaline phosphatase, when they originally tested, that is 760. So that's quite high with an elevated GGT. There are no baseline values that were available to review. She had mild elevations in transaminases, no eosinophilia. So this is another one where she recovered several days later. It was assessed as possibly an idiosyncratic reaction by the reporting physician. It resolved. Again, whether it was truly drug-related or not I'm not sure we can tell.

But those were the cases that the FDA had selected, and you'll hear more about them. If they have any additional information, we can discuss them then. But again, this is a fairly small number of cases, not all of

which we have sufficient information to really make a call as to whether it's truly drug-related. One clearly wasn't, the hepatitis A case, but the other cholestatic ones are reversible, relatively mild to moderate in intensity, and no sequelae.

DR. LEGGETT: Dr. O'Fallon.

DR. O'FALLON: Obviously, the ascertainment of adverse events does depend upon the diligence with which the data are collected. And the protocol apparently asked for them to be submitted real-time, on-line, and all that. But there was some suggestion in the FDA packet that in fact many of these adverse events were actually submitted in batch at the end of the study. Is that true? And if so, what kind of percentage of the adverse events were reported in batch instead of in real time?

DR. LEROY: The objective of the adjudication was to -- the process included first contact with the investigators by physicians from Aventis to make sure that all the algorithm possible was implemented at the source of the data. The clinical event committee was not here to guide the clinical evaluation of the case. It would have been impossible. And this is not how the clinical event committees are operating. So, on the contrary, all the information on the cases was gathered and all the information that was generated by the algorithm that was

discussed with the CEC before the study that listed a certain number of questions to ask and examinations to perform was gathered and submitted to the clinical event committees with clean data. And that's why they were submitted in batches.

So the speed was used here to go to the site and make sure that the patient had the appropriate examinations, and that's where we were making sure that all information was collected. Then all the packet was completed and provided complete to the clinical event committee.

DR. O'FALLON: So then basically you're saying that the adverse events were known to the company in real time but were reported to the CEC in batches, mostly.

DR. LEROY: They were to be reported in batches as predetermined in the protocol.

DR. O'FALLON: To the CEC.

DR. LEROY: To the CEC.

DR. O'FALLON: But to the company --

DR. LEROY: And to us it was on an on-line basis, yes.

DR. O'FALLON: Okay.

DR. LEGGETT: Sort of looking at the time, I'll ask Dr. Brown to give a quick question, and then I would like to ask a quick question, and then we're going to take

a break.

DR. BROWN: We've heard nothing about anaerobes this morning, and so I need to ask. Non-first cases of sinusitis are frequently associated with anaerobes, and anaerobes are obviously important in the stool. So I'd like to hear something about the effect of this drug on stool anaerobes and sinus anaerobes.

DR. LEROY: I will ask Dr. Jenkins to answer this question.

DR. JENKINS: The activity of telithromycin against anaerobes is mixed. If you take a look at the range of MICs, generally we see that telithromycin is less active against the gut anaerobes, the Bacteroides fragilis group. This looks at ranges of MICs, but the MIC 50 for B. frag is in the range of 2 to 4 micrograms per ml. Whereas, if you take a look at the activity against the oropharyngeal anaerobes, the Peptostreptococci, the Prevotella species, and so forth, typically the MICs for these organisms in fact are quite low. The ranges don't really do it justice, but the MIC50 for Peptostrep is in the range of around .25 micrograms per ml and the MIC50 for the Prevotella species likewise is in the range of .25 to .5 micrograms per ml. So the short of it is it has better activity against oropharyngeal anaerobes than it does against gastrointestinal anaerobes.

DR. LEGGETT: I have a couple of questions for Dr. Jenkins or any of your experts. I would like to get some clarification about the establishment of the breakpoints. The company, I believe, is calling for a breakpoint of 1, whereas the FDA in the briefing document had a lower breakpoint. That would obviously have some impact in regards to your slides 18 and 22, as well as Dr. Leroy's slides of 35 and 36.

DR. LEROY: I think that we've clarified with the FDA that it was the breakpoints of the previous document and that will be discussed at the NCCLS, given the fact that all the strains above 0.25 were cured.

DR. JENKINS: We will be making our presentation to the NCCLS for antimicrobial susceptibility testing breakpoints on Tuesday, and the breakpoints that we've used in these discussions are consistent with those that we will be requesting based on population distributions of organisms, pharmacokinetic data, PK data, PD data, and also the clinical cure rates for the more serious indications.

DR. LEGGETT: And finally, for Dr. Bhargava, can you tell us some information about how endothelial lining fluid levels correlate with clinical cure? I mean, we're given numbers, and he made the statement that it was correlated with extracellular fluid, but that's not quite

the case. Interstitial fluid should be in equilibrium with serum. So I'm a little confused about that.

DR. LEROY: I don't think that we have data showing correlation and I don't think that any other sponsors have done this exercise in these type of studies. What we have here is that the studies were performed in a laboratory that is used to doing those studies, Honeybone and Weiss, that has done those studies in fact for azithromycin and clarithromycin, allowing a comparison.

What we have with this compound is a very good balance between the serum levels that are between 2 and 3, the epithelial lining fluid level, according to the methodology of Weiss with a peak at 14, and the macrophage levels that are over 100.

To answer your question, back to your question, we didn't perform a correlation between the ELF and --

DR. LEGGETT: So it's still a hypothesis basically.

DR. LEROY: It's still a hypothesis, yes.

DR. LEGGETT: Thank you.

Now, I would like for us to take maybe a 10-minute break.

For the committee members, I'm trying to get the FDA's thing done this morning, so that our lunch could be shorter if we all agree to eat at the buffet. So, let

me know during the break. And we'll come back in 10 minutes. Thank you.

(Recess.)

DR. LEGGETT: Hello again. I would like us to get started since we're only an hour and 10 minutes late.

This next portion will be the FDA presentation. I would like to get through this and questioning before we take a break for lunch. We'll start off with John Alexander who is going to give us a presentation about the efficacy of telithromycin.

DR. ALEXANDER: Good morning. Unfortunately, I'm not going to be able to make up an hour and 10 minutes' worth of time, but I'm going to try and go through this as quickly as I can.

My outline is that I'll go through the presentation of efficacy for each of the separate indications, and what I've done is highlight the original NDA submission and the results that you've seen previously in the April 2001 advisory committee meeting in blue, and then any new information that we received is highlighted in yellow in studies that were in the resubmission. I'm going to try and go through those quickly so that we can get to talking about drug resistant Strep. pneumoniae, especially those patients with community-acquired pneumonia due to DRSP.

So the three indications for which the sponsor is seeking approval in this resubmission are acute exacerbation of chronic bronchitis, acute sinusitis, and community-acquired pneumonia. The studies of tonsillopharyngitis were done as part of the original submission. That information is part of the FDA's briefing package, the appendix the you received as a briefing package back in April, but we're not going to discuss those today.

For acute exacerbation of chronic bronchitis, there were a total of three studies done. Two were provided within the original NDA submission, studies 3003 and 3007, and there was one additional study provided for the resubmission. All of those three studies were fairly similar in design.

The results of clinical outcome of the test-of-cure visit for the per-protocol population and the MITT population are shown here. These results are basically consistent with the results seen by the sponsor.

One note here is that for study 3003 the FDA used a 97.5 percent confidence interval as a statistical adjustment for an interim analysis that was done in the study.

Looking at clinical outcomes by pathogen for acute exacerbation of chronic bronchitis, these are the two

studies that were in the original submission, study 3003 and 3007. One note to make here was with the telithromycin clinical cure rates for patients with H. influenzae which was part of the concern that the FDA had and why within our approvable letter we asked for submission of an additional study of acute exacerbation of chronic bronchitis.

These are the results for that study 3013 of clinical outcome by pathogen. What you see in this study is a clinical outcome for Haemophilus influenzae of 77.1 percent with a greater number of isolates here.

Moving on to acute sinusitis, there were three studies that were presented within the first review cycle, and there were no new studies in the resubmission. Study 3002 was a study that compared 5 days to 10 days of telithromycin and was otherwise uncontrolled. This was a study that included microbiology. Study 3005 compared telithromycin to amoxicillin-clavulanate in a study that was based on clinical diagnosis and only had microbiology obtained in a small group of patients.

Study 3001 compared telithromycin to cefuroxime axetil and this study had a microbiology obtained by sinus puncture within the United States and obtained by endoscopy within other countries. So each of these studies is slightly different from one another.

When we look at the results that are shown

here, this is the clinical outcome at the test-of-cure visit for the clinical per-protocol population, the bacteriologic per-protocol population, and the overall MITT population.

In answer to Dr. Cross' question earlier, part of the reason that you might see a higher cure rate in the per-protocol clinical population for study 3002 is because that comparator that's listed there is 10 days of telithromycin. So no matter which arm of the trial that you were in, people knew that patients were receiving telithromycin so there might be some bias towards reporting a higher outcome rate.

With the other study, study 3005, where the rates are lower, there we don't really have an explanation as far as the reason for lower outcomes, but this was based on a clinical diagnosis and not based on bacteriologic diagnosis in most of those patients.

Moving on to the by-pathogen cure rates, these are the three main pathogens for acute sinusitis. These are the clinical outcomes that were seen at the test-of-cure visit for patients who had these pathogens isolated at baseline by sinus puncture and separately are shown the telithromycin 5-day, 10-day, and then the two comparators.

Moving on then to community-acquired pneumonia, within the original NDA submission there were three

comparative studies that were done and three open-label studies. One note here, the study 3009 that used the comparator of trovafloxacin was stopped early, as noted previously by the sponsor.

These results here show the clinical outcome at the test-of-cure visit for the per-protocol clinical population and the MITT population. Again, these results are consistent with those shown by the sponsor earlier.

Looking at the specific pathogens identified at baseline, these are the clinical outcomes at the test-of-cure visit by the particular pathogen. This includes all Strep. pneumoniae.

Also shown here separately are those patients with atypical pathogens, Chlamydia, Mycoplasma, and Legionella. I would note here with the Legionella pneumophila that the patients, for the most part, were diagnosed serologically. There were 4 patients out of this group that had a diagnosis that was by urinary antigen.

So for new studies in the resubmission, there were three new studies that were provided. Study 4003 is a comparative study done in western countries. Study 3012 was an open-label study of telithromycin given for 7 days, and then there was a separate submission of a Japanese study of telithromycin. I'm going to talk about the Japanese studies separately from the presentation that I

make about the western studies because the designs of these studies really are a bit different from the designs of the western studies. So I present the information that's obtained from DRSP separately.

Now, since the goal of the resubmission was to address questions of the activity of the drug for drug-resistant Streptococcus pneumoniae, that's what the rest of my presentation focuses on.

So clinical cases of patients with drug-resistant Strep. pneumoniae were collected for patients for both CAP and sinusitis, and these were the definitions that were used for penicillin resistance and erythromycin resistance.

One thing that I wanted to note before we get into the actual clinical outcomes are the results of in vitro studies, and what I've done here is taken the patients who had community-acquired pneumonia that were the per-protocol population and separated the patients who had either erythromycin-sensitive or intermediate strains from those who had erythromycin-resistant Streptococcus pneumoniae. What I show is the telithromycin MIC. Now, what you see is a slight shift upward in terms of the telithromycin MIC for those patients who have erythromycin-resistant versus erythromycin-sensitive strains, but we don't necessarily know what, if any, clinical significance

this has.

So moving on to community-acquired pneumonia due to drug-resistant Strep. pneumoniae. There were a total of 49 cases of CAP due to DRSP from the western studies. I'll also get into briefly the subset of bacteremic cases and the additional cases from the Japanese trial.

Now, what the sponsor had focused on previously was what the bacteriologic per-protocol population was and the outcome that's there. I want to focus a little bit on the MITT population and talk about the difference between the evaluable and the subjects that were non-evaluable.

Among the non-evaluable patients, there were 5 patients who were categorized by the investigator as success, 2 who were categorized as failures, and 5 that were indeterminates. Now, among these patients, none of these patients in my estimation had a misdiagnosis of community-acquired pneumonia. They all had clinical and radiologic criteria that met that. Some of the reasons for non-evaluability related to whether the sputum specimen was qualified as adequate by a Gram stain or not, but in most of those cases I did think that Strep. pneumoniae was still the likely pathogen within the cases.

With the 5 indeterminate patients, there was 1 patient who was withdrawn for an elevated BUN and

creatinine. That was his baseline BUN and creatinine was elevated, and that was part of the exclusion criteria, but the patient didn't follow up again until day 6 and at that patient seemed to be doing well and was switched off therapy to something else. And I would categorize that as a patient who truly had an indeterminate outcome.

For the other 5 patients who were categorized as indeterminate, there was 1 patient who had bronchitis that was diagnosed at the test-of-cure visit and started on other antibiotic therapy.

There was 1 patient who was on therapy and had a sudden increase in labored respirations, transferred to the ICU, was felt by the investigator to have a suspected aspiration, and ended up dying on day 5 of therapy.

There was another patient who was started on new antibiotics on day 3, citing a baseline blood culture that was positive for Streptococcus pneumoniae, but the patient was also experiencing some adverse events as well.

The final patient was a withdrawal for personal reasons. This patient completed his entire course of telithromycin, came to the end-of-therapy visit, seemed to be doing well, 2 days later withdrew from the study due to personal reasons, but then 4 days after that, there's an AE form that's filled out that indicates that the patient had a recurrence of pneumonia. So that's within the test-of-

cure visit window, and the patient actually ended up dying 2 days later.

So from my standpoint, for all PRSP -- so this is those patients who have either PRSP with or without macrolide resistance -- the outcomes that were seen as far as clinical cure at the test-of-cure visit is a rate of 70.4 percent, and then for all ERSP, regardless of the penicillin resistance, it's 78.4 percent.

For comparator patients within the controlled studies, there were 7 comparator patients who had drug-resistant Strep. pneumoniae. Two isolates were susceptible to the comparator agent. So there was 1 PRSP that was treated with clarithromycin that was erythromycin-sensitive, and 1 erythromycin-resistant but penicillin-sensitive strain that was treated with amoxicillin.

Interestingly, there were 5 patients who were treated with clarithromycin within the controlled studies that had erythromycin resistance, and the outcome in those is 3 out of 5 clinical successes.

This looks at the subset of patients who had bacteremia and shows again what the per-protocol population and the MITT population results were.

And these results come from Japanese studies. Again, I decided to present these separately in part because of the fact that the study designs are somewhat

different, as well as the fact that you're talking about a different dose, 600 milligrams, in most of these patients. Some did receive 800 milligrams and the Japanese formulation that was used. These are the results that were seen. There weren't any bacteremic cases among these because bacteremia wasn't assessed within those trials.

And then finally for acute sinusitis, there were a total of 29 cases of acute sinusitis due to drug-resistant Strep. pneumoniae. These include both patients that had a 5-day duration and a 10-day duration of telithromycin treatment, and all these cases are from studies within the original NDA.

Again, what I'm showing here is the clinical outcome at the test-of-cure visit for those patients who had a baseline pathogen, separating out those patients who had just PRSP, those who had just ERSP, and then those isolates that were both penicillin- and erythromycin-resistant.

That's my presentation.

DR. LEGGETT: I think we'll probably take questions at the very end.

The next speaker will be Dr. Charles Cooper about telithromycin, an integrated summary of safety.

DR. COOPER: Thank you.

I'll start with my outline. First, we'll start

with a description of the safety database for phase III clinical trials. Then I'll give an overview of the safety-related events and then spend some time with specific adverse events of special interest, namely cardiac, hepatic, and visual, and then end with a summary slide.

Interest in the cardiac and hepatic risk profile was generated from data from preclinical and phase I studies, and interest in the visual risk profile arose from data from phase I and phase III studies.

This is an overview of the phase III safety database. This excludes the large safety trial, 3014. That's the 24,000-patient safety trial. That is excluded and will be discussed later in detail by Dr. Rochester.

As you can see, there are 1,207 new telithromycin-treated patients. Those come from three different trials and results in a total of 4,472 telithromycin-treated patients.

The treatment groups were balanced for age, sex, race, and weight. There were slightly more patients in the comparator arm who were over age 65, and there were 59 patients who were treated with telithromycin who were under age 18.

This table shows the deaths overall and by indication and by controlled versus uncontrolled, and they're similar between telithromycin-treated patients and

comparator. None of these deaths were thought by the investigator to be related to study medication.

This table shows nonfatal serious adverse events in controlled phase III trials. As you can see, they are relatively similar, slightly higher in comparator, but otherwise relatively similar between the two and mostly related to underlying disease.

This table shows adverse events in controlled phase III trials and shows that the most common adverse events in telithromycin-treated patients were gastrointestinal, and telithromycin-treated patients seemed to have a slightly higher rate than comparator-treated patients of gastrointestinal adverse events, as well as dizziness, although generally fairly similar.

I'd also like to point out at the bottom for blurred vision, for controlled studies there were 17 patients versus 2 in comparator.

With regard to adverse events resulting in discontinuation in controlled phase III trials, the rates were similar between the two treatment arms or between telithromycin and comparator, slightly higher rates for gastrointestinal adverse events resulting in discontinuation, but overall very similar.

With regard to the cardiac risk profile, preclinical and phase I studies showed that telithromycin

blocks IKr and prolongs action potentials in isolated fibers, also prolongs QT and increases heart rate in dogs. Also, there was shown to be a concentration-dependent increase in QTc in phase I studies. As well, as was described earlier, there is an increased exposure with patients with severe renal impairment with or without concomitant CYP3A4 inhibitors.

With regard to cardiac adverse events in controlled phase III studies, the rates are similar between telithromycin-treated patients and comparator-treated patients, a slightly higher percentage of patients with palpitations in the comparator-treated arm, but otherwise very similar.

On the right of the slide, you will see a list of all the causes of the serious cardiac adverse events in telithromycin-treated patients. On the left, we see it broken down according to controlled versus uncontrolled studies. And below that, we see the rate for comparator. Roughly similar, and none of these were thought to be related to study drug by the investigator.

ECG data from phase III clinical trials includes additional data from one of the new studies, which was 3013. The two other new studies didn't consistently collect ECG data and therefore wasn't incorporated into the original data. The incorporation of the new data from 3013

did not result in a significant change in what was concluded from before. There was a mean on-therapy change in QT increase of 1.5 milliseconds. And when compared to telithromycin in those controlled studies in which clarithromycin was used as a comparator, we see an increase of 3.8 milliseconds for telithromycin and 3.3 milliseconds for clarithromycin, but there was quite a wide interval there. Roughly similar.

With regard to hepatic risk profile, preclinical studies demonstrated hepatotoxicity in rats, dogs, and monkeys, increased transaminases, and hepatic necrosis in a 4-week rat study, also hepatocellular hypertrophy and multi-nucleated hepatocytes were seen. Hepatic effects of telithromycin were assessed to be greater than that of clarithromycin in animals.

Hepatic toxicity seen in study 1030, one of the phase I studies, was shown in 8 elderly subjects who received doses of 1,200, 1,600, and 2,000 milligrams of telithromycin or placebo. Three of the subjects experienced increases in transaminases in the 100 to 300 range, and if you look at the subjects, you'll note that there is a 7-day, a 17-day, and a 14-day delay in the onset of these increases in transaminases suggesting a possible latency period.

This table shows the hepatic adverse events in

controlled phase III studies. Roughly similar between telithromycin and comparator for the different adverse events that were reported.

There were 4 patients with serious hepatic adverse events, 3 in the telithromycin arm, 1 in comparator. Drug effect was unlikely in one of the telithromycin patients and in the comparator patient. Drug effect was thought to be plausible in 2 of the telithromycin patients. One was a 76-year-old woman who was also on pravastatin. The patient was asymptomatic and had an increased transaminase on telithromycin, but recovered without sequelae.

The second patient is a 53-year-old male with eosinophilic hepatitis that you heard about earlier, and I'm going to go into a little bit further detail about this patient in the following slides.

The patient is a 53-year-old male with asthma and diabetes. The medications are listed here. The patient was treated with a 10-day course of telithromycin for CAP and received six doses of acetaminophen beginning approximately around day 13. On day 14, the patient experienced fever, vomiting, and diarrhea. You can see the table shows the laboratories during the course of the adverse event. The patient began with an elevated ALT of 81 and then after treatment with Ketek, or during the

course, developed an increase in transaminase with the ALT peaking at 1529. Eosinophils were also elevated at baseline and also increased over the course.

On day 23, this patient was hospitalized for hepatitis and serologies for viral etiologies were negative. A liver biopsy was done on day 29 which revealed centrilobular necrosis and eosinophilic infiltration. By day 94 LFTs were virtually normal.

At follow-up on routine testing, the patient was asymptomatic, but 9 months after the event was found to have ALT that was increased to 1331 and a total bili that was also increased. Again, serologies for viral etiology were negative and an anti-smooth muscle antibody was positive at 1 to 1,000. There was no eosinophilia.

A second liver biopsy was done and revealed zone 3 and portal fibrosis, piecemeal necrosis, a plasma cell infiltrate, consistent with autoimmune hepatitis.

This slide shows changes from a normal baseline for patients in controlled CAP studies who began with a normal ALT and tracks the number of patients who then developed increases in ALTs according to severity. As you can see, there's a slight increase in the telithromycin arm for increases in ALT below 5 times the upper limit of normal. This pattern was seen in the original submission, and when the new data from the new study was incorporated,

the pattern persisted.

And now for information on the visual risk profile, blurred vision in phase III studies was seen in 20 out of 4,472 telithromycin-treated patients versus 2 in the comparator-treated patients. In controlled studies, there was a rate of 0.6 percent versus 0.1 percent for comparators. You can see for females the rate was 0.9 percent, whereas for males it was 0.4 percent, thus suggesting an increased rate in women.

We looked at whether the presence of a 3A4 inhibitor affected the rate of blurred vision in phase III studies. I want to stress, before talking about these numbers, that this is an exploratory analysis. Patients were not randomized according to 3A4 inhibitor intake, and therefore conclusions may not be able to be drawn and much care needs to be taken in looking at this data.

When we look at patients who received a CYP3A4 inhibitor, 1.9 percent of patients who received telithromycin had blurred vision versus 0.4 percent for patients who did not receive a CYP3A4 inhibitor. 15 of the patients had mild blurring, 4 with moderate blurring, and 1 with severe blurring. The median duration was 2 days and the median onset was on the second day. The range of duration was between 1 and 10 days, and the range of onset was on day 1 up to day 6. Most of these patients remained

on study drug.

There were 5 discontinuations due to visual adverse events, 4 of which were in controlled studies and appear to be related to this mechanism of blurred vision.

There were two phase I studies, 1059 and 1064, that looked at telithromycin-associated visual blurring. There was an incidence of 13 to 50 percent in subjects who received 2,400 milligrams of telithromycin, and the incidence seemed to be higher in younger subjects. The median onset was 3 hours with a range of 1 to 5 hours, and the median duration was 2.8 hours with a range of .9 to 20.3. It appeared that the blurred vision was at least in part likely due to interference with accommodation.

There was one serious visual adverse event in a patient in study 3005. It's a 42-year-old female who had a serious adverse event of unable to accommodate. The adverse event was determined to be significantly disabling and began 2 hours after study drug administration. The patient was seen by an ophthalmologist who gave a diagnosis of unable accommodate. The adverse event was initially assessed as related to study drug. Telithromycin was discontinued, and the adverse event resolved. Later the causality of the adverse event was changed to not related to study medication.

In summary, overall the most common adverse

events for telithromycin are gastrointestinal in nature.

Phase I and preclinical studies show a concentration-dependent QT, and there were no drug-related serious cardiac adverse events.

Hepatotoxicity was seen in preclinical studies, and there was a cluster of patients with increased transaminases in phase III. There was also a slightly increased incidence in low-level ALT elevations in phase III. There was 1 patient with eosinophilic hepatitis in phase III.

The incidence of blurred vision was found to be 0.6 percent in controlled studies and appeared to be higher in females. This adverse event is thought to be possibly, at least in part, due to interference with accommodation.

And that's the end of my talk.

DR. LEGGETT: Thank you. Again, we'll take questions at the end.

The next speaker will be Dr. George Rochester who's going to talk about study 3014.

DR. ROCHESTER: Today I would like to present some of the basic findings and discuss some of the design issues related to the large comparative safety trial conducted in a usual care setting. Of course, sometimes when we think about planning these large, so-called simple trials, they sound simple but in trying to execute them,

certainly there are many issues that do come into play. So I will address some of those issues as I go along.

Study 3014 was a randomized, comparative, open-label trial, and it would appear that the randomization scheme was carried out properly. Both treatment arms were similar in terms of any subgroup characteristics that one could look at.

It was designed to look at safety in community-acquired respiratory tract infection patients, which is not the same as just safety in healthy patients. This cohort consisted of three groups: patients with community-acquired pneumonia, AECB, or acute sinusitis.

And certainly when we use the term "24,000 patients," what we really mean is we've got 12,000 patients in each treatment arm. So essentially there were 12,000 patients on telithromycin.

Telithromycin was given for 5 days for the treatment of sinusitis and 7 to 10 days for CAP or AECB, and we've heard that although a claim is requested for treatment of AECB of 5 days, in this study 7 to 10 days therapy was used in order to gain further safety information on the longer duration of therapy given that at the time of planning the study we had a smaller database of 3,265 from the previous submissions, and there appeared to have been an increased number of adverse events seen in CAP

which was the group that received the longer therapy.

And our comparator here is amox-clav, which was given for 10 days for all three indications.

The usual care setting. What that means is we've got very relaxed inclusion and exclusion criteria, so we could get then a very heterogeneous, more real-to-life sort of population that we hoped would reflect the population to which the drug would be given, should it be approved.

In terms of how these indications were distributed, we had a target set up to get about 40 percent of subjects with CAP or AECB, and the study exceeds that. I think we had about 46 percent.

Also, we wanted at least 35 percent of the subjects should be above age 50, with a goal of getting more information in the elderly, particularly those over 65. Again, the study exceeded that number. We had probably about 25 percent of the subjects over 65, and almost 1,000 in each treatment arm were over 75 years of age.

We also wanted subjects with concomitant illnesses. So we included subjects with cardiovascular disease for obvious reasons, renal or hepatic impairment -- there is probably about 1 percent, maybe 100 or more subjects in each group with these conditions -- and with

significant concomitant drug use, such as subjects taking drugs that inhibit or are metabolized by the CYP3A4 or CYP2D6. Again, we had, in terms of concomitant drug use, about 1,500 subjects that were taking a CYP3A4 inhibitor.

The study was designed with four adverse events of special interest in mind. The hepatic which was defined as a clinically overt presentation of significant hepatic injury, an ALT of greater than 3, a total bilirubin of greater than 1.5, and worsening of a preexisting hepatic condition. So the patient had a baseline hepatic problem, but on therapy or during the study period, if that worsened in intensity or, for example, required a prolongation of hospitalization or produced hospitalization, that would have been considered an adverse experience.

And then there were three others: cardiac, visual, and vasculitic.

Now, in trying to size the study, we basically thought there was about 1 case in almost 4,000 patients, and so we accepted 12,000 patients as a good effort. The study was not powered in the sense of being able to simultaneously rule out all four adverse events of special interest. So most of the data then was driven by the hepatic situation.

What do these overall adverse event rates -- how reassuring did these kind of make you feel? In the

phase III trials, generally we were seeing about a 50 percent adverse events rate. In study 3014, there were many subjects with comorbidities such as diabetes, renal impairment, and so on, which was quite enriched in terms of at-risk subpopulations, many of them on concomitant drugs. In this study what we saw is an overall adverse experience of about 23 percent which is just about half of what we've seen before, which in my mind is a little bit surprising. I can't tell you exactly what number to expect in that. I just know that when you look at a mixture of patients in this kind of cohort, one would expect the adverse events rates to be slightly more similar to what we've seen before.

Again, in this study only 10 percent of the subjects did have CAP, and we understand that there could have been more heterogeneity in terms of the population that was studied here versus what we've seen in previous trials.

The adverse events rates, when you look at the various subgroups -- and all these subgroups are subgroups that we anticipated when the study was designed. What we've seen is an overall, again, 23 percent in both arms. We've seen that if you look at age greater than 65 years, hepatic impairment, generally cardiovascular disease as a group, and CYP3A4 substrates or HMG CoA inhibitors,

basically you're seeing rates similar to comparators.

If one looks at severe renal impairment, it will look different from the sponsor's numbers in the sense that this group is not just all patients considered to have had some renal impairment, but these were the ones documented with less than 30 mls per minute of creatinine clearance. There were 23 patients that were in that group. 5 of them had an adverse event. In the comparator group, 17 such patients, and there were no adverse events reported there.

If you look under cardiovascular disease, particularly the ones who had a history of congestive heart failure, there were 277 patients and an adverse events rate of about 30 percent. If you look at the comparator group, a similar number of patients, about 270, and that rate was about 24 percent, which is similar to the overall rate that we've seen in the population.

The way in which these hepatic events were supposed to be investigated. Visit 1 on day 1, which is the start of study medication. All subjects were going to have basically a panel of hepatic labs. And all subjects were to report to a clinic visit on day 17 to 22 for their follow-up, and at that point they were also going to have a repeat lab.

Now, any subjects who had, for example, a 3

times the upper limit of normal change from baseline in their ALT values were flagged as potential hepatic adverse events of special interest, and these subjects were to be followed carefully and followed obviously to resolution. That group consisted of about 209 patients, 110 in one group and 98 in the other.

Follow-up was to be up until return to baseline or sufficient decline. Sufficient decline is basically defined as return to about 1.5 times the upper limit of normal if you started with a normal baseline and 2 times the upper limit of normal if you started at an abnormal baseline. Most of the subjects in this study, at least in this group, were followed up for 6 months, which I think was quite impressive in the sense that of 209 subjects, we had essentially complete follow-up information on all but 13. Three patients had died not from a hepatic-related event, but they had died. Therefore, we had partial information on those. And 9 subjects out of the other 10 were in the telithromycin arm, and they refused follow-up. Essentially they said they have no symptoms, they're fine, and they didn't want to continue in the study.

Now, one way that this study could have significantly been improved -- during the design of the study, we talked about implementing some management algorithms that would guide investigators with respect to

the minimum expectation for follow-up of adverse events of special interest. This could have minimized obviously missing critical data and improved completeness of case documentation during the conduct of the study. In other words, we recognize that in any trial we've got quite wide variability in terms of follow-up of subjects by investigators. Some are very diligent; others may not be so diligent. Investigators have different medical specialties and interests and therefore they may follow patients differently. And that's to be expected in the usual care setting, and in that setting we understand that.

However, there's a difference between just the usual care setting practice and a clinical trial. A clinical trial still needs to have a little bit more structure. So this was something that we did emphasize. In the actual carry-out of the trial, this was certainly not a major thing that was emphasized.

Of course, that does pose some limitations in terms of asking questions like, how long did it take the patients to achieve maximum change in LFT, the time course of the subjects? You follow them over time and you want to find out how long it took them to resolve or to return to their baseline status. And because that data is not collected in a systematic way, it poses very difficult issues in terms of analysis and/or interpretation.

Adjudication was explained before. It should be done blindedly, and it was done by the CECs. They were planned to be at regular intervals, about biweekly intervals. It was largely done in batch at the end of the trial.

Hepatic AEs were followed to resolution. Of the 209 subjects that were in this group, most of them had lab recovery. All of them, except just about 9 or 10, did not have complete follow-up information, and I explained that before.

What are the changes like among subjects who had normal baseline ALT values? In this version of our PowerPoint, we get donuts, but actually these mean greater than.

(Laughter.)

DR. ROCHESTER: I suppose you become greater than if you eat donuts.

(Laughter.)

DR. ROCHESTER: So here we've got subjects who are less than or equal to 1 time the upper limit of normal. So they retain their baseline status. Essentially the majority, over 90 percent, of these subjects are in that group. You'll find that telithromycin looks fairly similar up until you get to about greater than 2 times. Greater than 2 times, you begin to see numbers, about 35 compared

to 22, 12 to 8, and as you get above 8, you begin to see numbers like 7 to 2. Again, these are very small numbers. However, you're seeing this trend always that on the one arm that always exceeds the other, it's the telithromycin arm.

If you look at the late post-therapy, these are subjects who were followed up greater than 35 days. Again, here you'll see fairly similar up until about 3 times. When you get above, say, 5 times the upper limit of normal, there's 4 compared to none, 8 compared to 3. So slightly more patients in that group. Again, not large numbers of patients.

Changes in AST. It was a similar picture. Somewhere between 5 and 8, there were 5 in teli, 1 on Augmentin. If you looked at greater than 8, 5 in teli, 1 on Augmentin. They're smaller numbers, but you just consistently see on the telithromycin arm that there were more patients there.

Changes in hepatic analytes at any post-therapy time point. Greater than 3 times ALT I've already mentioned. Greater than 8 times, at any time point, again you saw about 19 subjects here, twice as many, 10 in the other arm, that you would see on Augmentin. Here, of course, we've got subjects with an ALT greater than 3 and a total bili of greater than 1.5. There were only 3 here on

telithromycin, and of course, there were 6 on Augmentin.

Combined ALT and bilirubin changes at any post-therapy time point. Again, the numbers showed for telithromycin here they were a little bit better in the sense that for ALT greater than 3, total bili 3 to 6. Patients were having those same changes but without increase in alk phos, 1 on telithromycin, 4 on Augmentin. And there were no cases on telithromycin that had transaminase elevation; in addition, jaundice without an increase in alk phos.

If you look at 10 days versus 5 days of therapy -- and these numbers to me were quite similar, 7 to 5. Greater than 8, there were 5 to 2. Essentially I didn't see anything major here in terms of 5 days versus 7 to 10 days of telithromycin.

Subjects who met a hepatic endpoint definition. Essentially the cases that were adjudicated, we have the same numbers. There were 3 here. There were 2 in the other arm. Yes, there's overlap in these confidence intervals. You'd probably expect around 7 cases in 10,000 exposures to meet an endpoint definition such as was used in this study on the telithromycin arm.

A couple of cases that I just wanted to go through quickly. One case was a 60-year-old female treated for 7 to 10 days telithromycin for AECB. The patient had a

past medical history that included recurrent cystitis and asthma. Medications included Bactrim. The patient remained asymptomatic. Baseline LFTs were normal on day 1, day 17. On day 25, reported an ALT 3 times the upper limit of normal and AST 2.5 times. On day 29, ALT continued to be up to 7 times the upper limit, which reached a maximum value of 10 times the upper limit on day 36. AST also reached max of 5 times the upper limit. Serologies were negative, and ANA and smooth muscle antigens and so on were all negative. There was some eosinophilia seen in this case. This was again at about day 36, and ANA was positive at that time point, 1 in 160 dilution.

The patient was then treated with prednisone. This was a case of a patient who, I guess, was determined to go on vacation and convinced her physician to give her some treatment rather than further biopsy or any other thing. This patient went on to have prednisone treatment, was adjudicated as clinically well and possibly related to study drug. This was by the committee.

Another case, 3440-001, a 75-year-old white female treated for acute sinusitis, received 5 days. A history of cholecystectomy, coronary artery disease, hypertension, and some degenerative joint disease. No history of anything concerning liver disease, and negative for alcohol intake.

The patient did have in her concomitant meds Tylenol, which she took p.r.n. Four hours after her last dose, she had a Tylenol level of 2 and an upper limit for a toxic range would have been greater than 150.

Day 18 she presented with severe epigastric pain, right upper quadrant tenderness, fever of 101 degrees Fahrenheit, jaundice, and fatigue. She had a CT scan which was negative for gallstones, negative to duct dilatation. On day 18, she had her maximum change between 8 to 15 times the upper limit of normal in ALT. AST was 21 to 37 times the upper limit of normal, a doubling in her alkaline phosphatase, and a total bili of about 1.8. By day 29, all these labs were resolved after a 4-day hospital course.

It was considered a clinically serious event by the investigator and ruled as probably drug-related but passage of a stone cannot be ruled out by the CEC adjudication.

And the last case I'd like to talk about is a 72-year-old male treated for 7 to 10 days of teli for CAP. The patient had an underlying history including diabetes mellitus, hypertension, coronary artery disease. Negative for liver disease or for alcohol intake. The medications, did use Tylenol p.r.n.

Symptoms on day 30, presented with jaundice. This patient was also treated with Levaquin. On day 1, had

normal baseline status. Day 23, ALT 8 times the upper limit of normal. Alk phos 5 times and t. bili about 5 times the upper limit of normal. On day 29, those repeat labs were ALT 5 times, AST 3 times, alkaline phos 4 times. Total bili was reduced from 5 to about 4. Direct bili was 6.5 times. Eosinophils were within normal limits and all the serologies were negative. A CT scan showed a gallbladder with low density calculi and sludge. I think this patient also had an ERCP which did show sludge.

This case was one that went on to liver biopsy, had a cholecystectomy done, and that will be discussed later by our guest consultant.

By day 58, the patient appeared to be clinically resolved, and the adjudication committee thought this was possibly drug-related. Passage of a stone probably cannot be ruled out in this patient as well.

So in summary, regarding the hepatic adverse events of special interest, yes, they were uncommon, occurring in just about 1 percent of subjects being treated in both arms.

Telithromycin appeared to be similar to Augmentin with elevations in hepatic analytes, specifically ALT, up to about 3 times the upper limit of normal. More extreme elevations, such as greater than 8 times the upper limit of normal, were slightly more common among

telithromycin-treated subjects and consistently so.

A minority of subjects were symptomatic in both treatment arms.

There were no cases of liver failure or deaths among hepatic cases.

And at the 6-month follow-up time point, no subjects were reported with known sequelae. One telithromycin subject had persistent right upper quadrant tenderness on examination even at the 6-month time point follow-up.

That concludes my presentation.

DR. LEGGETT: Thank you.

The next speaker will be Dr. David Kleiner who will give us a discussion of the hepatic pathology.

DR. KLEINER: This is me. I'm from the Laboratory of Pathology at the NCI. I've been their hepatic pathologist and the sole hepatic pathologist for the last decade, and I'm also Section Chief of the Postmortem Section.

So what I'm going to do is show you some of the pathology from the 2 patients who have had liver biopsies in suspected cases of telithromycin hepatic injury. The purpose of the pathologist in this is twofold. One is to characterize the pattern of injury that we see to put it in categories so that we can form differential diagnoses, and

the second is to formulate an opinion as to what the etiology might be.

So the first patient I'm going to talk about is the one that was presented in 1999 and had two biopsies. You've already seen some of this data presented. This is just to sort of remind you of the time course of events and where the biopsy came in relationship to the therapy period and the profile of aminotransferases. The biopsy came about day 26 or 27, already on the down slope of the ALT peak.

What we saw -- or what I saw -- was primarily what I would consider zone 3 necrosis and inflammation. What you see here in this sort of moderate power shot are two central veins surrounded by a zone of hepatocyte necrosis and inflammatory cell infiltration.

If we come up closer, you can see the residual central vein here in the middle, a mixed inflammatory infiltrate composed of eosinophils -- and they're fairly prominent and scattered all the way through -- pigmented macrophages and lymphocytes and plasma cells.

Here's just another shot showing a particularly large cluster of eosinophils.

Although the degree of portal inflammation was very mild, there was some portal inflammation in many of the portal areas, along with a little bit of disruption of

the interface.

There was no Masson's stain supplied with the case, but there was another connective tissue stain, a van Gieson's stain, which stains collagen this pink color and kind of gives a sort of a yellowish color to the hepatocytes. So this is a central vein here showing infiltration of the vein wall by inflammatory cells and destruction of hepatocytes around it, but you see no increase in collagen other than what we would expect normally, so there's no central fibrosis at this point.

Nor was there any discernible periportal fibrosis. Here's a portal area, again the collagens in pink. So this is what one would normally expect. There is inflammation at the interface which is expanding the portal area that way, but no fibrosis yet.

So in terms of the pattern of injury, I would characterize this as a zone 3 centrilobular necrosis pattern with a mixed infiltrate of eosinophils and plasma cells, lymphocytes, and macrophages. There was moderate interface hepatitis and no significant periportal or sinusoidal fibrosis and no cholestasis.

The differential diagnosis for zone 3 necrosis is actually much longer than this, but these are usually the major players that we think about just in general terms. Hypoxic/ischemic insults, veno-occlusive disease,

and drug or toxic injury is in the list. And the mixed infiltrate with prominence of eosinophils and plasma cells is strongly suggestive of hypersensitivity reaction, either one that given the patient's history, there could have been something there before that was very mild that was exacerbated. But in general I would not characterize zone 3 necrosis as the typical part of acute autoimmune hepatitis.

The patient then recovered from this acute episode and was followed up some months later with a random ALT value that showed elevated transaminases again and received a second biopsy. At that time although the biopsy was done in December, there were results from tests that were done in November. ALT was up around 1300. Total bilirubin was only slightly elevated. Immunoglobulins were increased. At this time an anti-SMA was measured, but ANA and AMA were negative, and the viral serologies were negative.

What was seen at this point in this liver biopsy was a pattern of chronic hepatitis. This is again a low power shot. You can see now some distortion of architecture with early regeneration. There's a fibrotic bridge actually that wraps around here, really tracking along central veins. There's a normal portal area off to the side here.

In this case this shows a portal area and a much more typical pattern for chronic hepatitis, lots of interface hepatitis, plasma cells, and other inflammatory cells in evidence, not so many eosinophils at this point.

This is a central vein, showing that there was persistent inflammation around the central vein, also kind of causing an interface hepatitis, if you will, where the fibrotic edge met the liver cells. But each central vein was surrounded by a large cuff of collagen.

There was also spotty necrosis out in the lobules, also consistent with the pattern of chronic hepatitis. In this case there was a Masson's stain, so one can see that there was bridging fibrosis present. This is a central vein up here and a portal area down here and a fibrotic bridge in between. There was expansion of other portal areas that were not caught up in bridges, but most of the central veins were involved in bridging fibrosis.

This is just a higher magnification around one such central vein showing the relatively thick cuff of collagen.

So the diagnosis for this biopsy, chronic hepatitis, infiltrate again, suggestive of an autoimmune etiology because of the predominance of plasma cells, marked inflammatory activity -- many of the edges were involved by interface hepatitis -- and bridging fibrosis.

And the fibrosis pattern is consistent with scarring that matches the injury that was seen in the prior biopsy. Most of the injury in the first biopsy was central and that's where we saw most of the fibrosis.

And then the second patient with a biopsy this year was just presented and again had elevations of transaminases and bilirubin following treatment with telithromycin and received workup and then biopsy and cholecystectomy at this point. As was mentioned, the gallbladder did contain stones and sludge, which of course complicates the interpretation of all of this.

But what was seen here was a bit of a different pattern from what we saw before. Here you don't see much from low power at all. There's a little bit of an infiltrate in this portal area, maybe a suggestion of something going around this central vein here, but very mild overall. Portal areas did not show much in the way of inflammatory cell infiltrate and little or no interface hepatitis. Many of the portal ares were completely devoid of inflammatory cells.

But once you started focusing on the central veins, what you saw was a pattern of spotty necrosis and bilirubin in canaliculi and in hepatocytes. It's a little bit hard to show on photo mics, but there's bilirubin right in that cell there and there and there and there. So you

can see this little bit of brown color.

I do have a higher magnification. And there there's bilirubin. So there's the cholestasis, and there were also little pockets of inflammation and occasional apoptotic hepatocytes.

There was fibrosis present as well. It was, generally speaking, sinusoidal fibrosis and it was present around central veins and expanding out of portal areas.

So I would characterize this pattern as a combined cholestatic and hepatocellular injury, albeit it mild, as well as sinusoidal and periportal fibrosis. And this I think is old and predates any treatment by this drug but goes along with the history of diabetes mellitus.

Etiologic differential diagnosis of combined cholestasis and hepatitis can include sepsis, acute large duct obstruction early in this patient, as well as drug and toxic injury. In fact, in terms of patterns, since we don't usually biopsy the liver to diagnose acute large duct obstruction, this comes up much more often in this differential but you have to keep these other things in mind.

Now, in deciding whether or not an injury is caused by a drug, what we teach our residents and what's taught in the AFIP liver course is methodology by Irey which considers temporal eligibility, exclusion of other

drugs, toxins, and diseases, a known potential for injury by the agent, a precedent for the injury pattern, whether there was dechallenge, which means you take the patient off the drug and then rechallenge, and any toxicologic analysis that might have been done.

Now, when you're dealing with drugs in clinical trials, as I frequently do at the NIH, a lot of this information is missing. You don't have a precedent. There might have been preclinical studies that you don't have available to you. So a lot depends on what the pattern of injury is and how much you can exclude for other causes.

You try and categorize that toxicity into these categories. Causative, where it's confirmed and absolute. We very rarely get this. Probable, where there's good circumstantial evidence without other conflicting evidence. A possible association, where it's consistent but other factors cannot be ruled out. Coincidental where you're pretty sure it's really just coincidence and the drug can be ruled out. And negative is you're absolutely certain that there was no association.

So the way that I would categorize these -- it's my opinion -- for the first patient, that this first episode was probable drug toxicity and that's based on the pattern of injury of centrilobular necrosis and the unusual and atypical appearance if one were to try to explain this

as just a flare of acute autoimmune hepatitis. Now, later on maybe persistent drug toxicity, but it's more likely I think that there might have been an underlying acute autoimmune hepatitis that was mild.

Then in the second patient, this is possible, but it's really hard to rule out that coincidental early acute large duct obstruction which just made it look like drug toxicity. But I think that the evidence for these things is equal and that this is certainly a possibility.

Thank you.

DR. LEGGETT: Thank you very much.

The final speaker in this session will be Dr. Charles Cooper with post-marketing information.

DR. COOPER: Thank you. I guess I'd like to start by just pointing out that when we review new drugs, it's not often that we have a large post-marketing safety database to look at. So we viewed this post-marketing data for telithromycin with great interest and viewed it as being very important.

All data has strengths and weaknesses. Post-marketing data is certainly no different. Its strengths can be in numbers, large numbers, but there are many weaknesses. Typically post-marketing data is accrued through passive reporting which can lead to under-reporting or reporting or recall biases. The numerator and

denominator are often and usually uncertain. And information is frequently incomplete, and the lack of detailed and complete information often confounds assessment of causality and association.

I'd like to just take a second and just tell you the data that we have and how we came about it. When the NDA was resubmitted in July, the sponsor submitted summary tables that gave summations of the numbers of each different adverse event and also gave line listings with some amount of information. However, from that information, we were unable to really come to an understanding of specific cases. So we requested that the company submit the actual Medwatch adverse event report forms, but in the interest of time constraints, what the company was able to do was to extract the narratives from all the Medwatch forms and submit them to us for our review.

The narratives are sometimes incomplete, sometimes contain conflicting information, sometimes are very difficult to understand, and this goes back to the point of incomplete information and difficulty in understanding the data.

One thing I would like to point out that I think is important to note, when looking at these post-marketing events, is what the reporting physician or

treating physician thought about the possibility of the adverse event being related to Ketek. I don't mean to imply that the opinion of the treating physician is definite or definitive in any way, but presumably the treating physician has a much clearer, more detailed, and more comprehensive understanding of these individual cases, certainly more so than what we can glean from reading these oftentimes inadequate or difficult to understand narratives.

First, I'd like to just point out that Ketek was approved in 2001 in July by the European Union. It's been marketed in several countries, including Germany, France, Spain, Italy, Brazil, and Mexico, and has been approved for indications as listed.

The FDA received safety data up until October 1st, 2002, and that includes approximately in the low 900,000 prescription range, roughly a million prescriptions. There is one ongoing post-marketing safety survey being conducted in Germany as well.

The data that we received from the company -- we also received a SAS transport file that contained data listings -- had data for 406 patients with post-marketing adverse events. 347 of the patients were reported through spontaneous reporting. 30 were through the post-marketing safety survey, and 29 of the patients were actually part of

sponsored surveys. For the purposes of this presentation, those patients and adverse events from those patients have been excluded.

When looking at the adverse events by country, the majority come from Germany, 218 patients. Next is Brazil with 99 and then Spain and France.

The distribution of prescriptions by country is that the majority were actually in Germany and Italy. By this point, when taking into account November and December, the majority are actually in Germany and France. But for our database, it's Germany and Italy.

When looking at the post-marketing cardiac adverse events, there were a total of 37 reported adverse events from 24 patients. This table lists those adverse events. Patients may have had more than one adverse event. This table also lists the number of serious adverse events.

At the bottom we see that reported case of torsades. I'd also like to present one additional case of torsades that just came to our attention in the last week or two, and that case was not actually part of the reporting period leading up to October 1st. It actually occurred after October 1st.

That patient was a 44-year-old male with no history of cardiac disorder who was treated with Ketek for

bronchitis beginning on October 2nd. The patient developed malaise and, on the way to a rheumatology visit on October 12th, developed symptoms and was evaluated. The information in this report is not very detailed. The patient was reported to be discovered in torsades. Countermeasures were reported to have been taken, and the patient supposedly recovered. The reporter considered the causation as highly probable.

The company apparently has attempted to contact the general practitioner who reported this case, and I understand that the general practitioner has not been cooperative and may have even retracted this adverse event for unclear reasons.

The second case of torsades that was actually shown on that table is a spontaneous report by a general practitioner via a company representative. The patient was a 59-year-old male, and he had a history of coronary heart disease, status post PTCA with stent implantation after an angina attack the previous year, a history of hypertension, a history of paraplegia, as well as hypercholesterolemia.

The concomitant medications are listed here.

The patient started treatment on either the 22nd or 23rd with Ketek for sinusitis and tracheobronchitis, and either on the 23rd or 28th, he experienced an episode of confusion which was

retrospectively considered to be an equivalent of syncope. An EKG was done at that time and was reported to be normal, as was blood pressure. Ketek was discontinued. So Ketek was discontinued either on the 23rd or 28th. It's a little unclear. There was a follow-up report that states that this event occurred on the 23rd rather than the 28th, and that follow-up report also states that treatment started on the 22nd rather than the 23rd.

On May 30th, while driving his car, the patient had some sort of episode and lost control of his car and found himself in the middle of a corn field. He was hospitalized and the EKG showed no abnormalities.

According to the patient's wife, Ketek was readministered during the time of the hospitalization and the patient was without symptoms until the next afternoon when the patient's telemetry monitor revealed what was reported in the adverse event narrative as classic torsades, persisting, finally changing to ventricular fibrillation that results in a 0 line.

There's also some mention of a premature beat that may have occurred.

This is the entirety of the electrocardiographic data that we have for evaluation of this patient. The strips were not in order, and the proper order is strip number 1 and then 4 and then 3 and then 2,

and I'm going to present them in that order.

Strip number 1. There's some artifact and what looks like sinus rhythm at 14:52 on May 31st.

Strip number 4 at 14:57 shows what looks like sinus rhythm.

And 27 minutes later, this is what the rhythm shows. Now, there is a 27-minute gap during which time we're not sure exactly what happened. We're not able to draw any conclusions about what happened during that time.

This is the next strip, and that's that case.

This is the report of the echo, for the most part normal.

The patient had elevated CK but CKMB was percentage-wise very low. Potassium was 3.6 and other values were reported to be within normal ranges.

With regard to hepatic adverse events, there were 42 reported adverse events from 18 patients. All of these are from Germany. This table shows the numbers of adverse events according to MEDRA Preferred Term.

There were no deaths in hepatic-related post-marketing adverse events. There were two liver biopsies. Many of the reports again lacked detailed information which is, like we discussed, not unusual for post-marketing adverse events.

Case number 1 was a 61-year-old female who,

according to the narrative we had, had a history of infective endocarditis who was on long-term prophylaxis. The exact drug that the patient had been on for prophylaxis at the time of this event was not stated in the narrative.

The patient was treated for 2 weeks with Ketek for sinusitis and tonsillitis. After treatment, the patient continued with fever and a work-up was negative except for increased liver function tests.

The admitting hospital physician suspected liver reaction as caused by Ketek. The patient underwent a liver biopsy. The date of the liver biopsy in relation to Ketek administration was not reported in the narrative that we have.

There was no information on alcohol use or ultrasound results, but the biopsy results are listed here. This is verbatim: "a focal fatty degeneration of hepatic tissue with moderate intrahepatic cholestasis, as well as mild inflammatory mesenchymal activity. No signs of malignancy or specificity. No typical histologic aspects of chronic viral hepatitis. The findings could indicate a nutritive-toxic genesis."

Case number 2 involves a 70-year-old with a history of COPD, diabetes, and status post Bilroth surgery. No history of liver disease or alcoholism was reported.

The patient was admitted on December 13th with

flu-like symptoms, productive cough and hemoptysis, and was started on treatment with Ketek for what was presumed to be COPD exacerbation. The patient completed Ketek on the 15th and was discharged on prednisolone.

The patient was readmitted on January 28th with cholestatic hepatosis, likely drug-induced by telithromycin. This is a verbatim report out of the narrative for the adverse event.

The results of the ultrasound are listed here.

The patient underwent liver biopsy on February 2nd, and this is the verbatim report in the narrative that we have for the results of that liver biopsy. "A marked cholestatic hepatopathy with mononuclear inflammatory infiltration in the periportal triangle with singular cell necrosis and surrounding granulocytic reaction. Morphol picture compatible with a cholestatic drug-toxic hepatitis as can occur after antibiotics."

I suppose I understand from what was said earlier that this patient received Augmentin. However, that information was not in the narrative that we have. The words amoxicillin and clavulanate are listed almost as a non sequitur in the narrative, but there are no dates associated with that. So it's unclear to us when he received that, but I understand from follow-ups, as stated earlier, that he may have received Augmentin.

Case of interest number 3. Well, first let me say we have, with these two biopsies and previous biopsies, what appear to be varying patterns, and we can discuss later what exactly this might mean with regard to the likelihood of drug-related hepatotoxicity as possibly mediated by telithromycin exposure.

Case of interest number 3 is a 33-year-old female with a history of pyeloplasty on oral contraceptives with no other past medical history. She was treated with Ketek from March 10th to March 14th, 2002 for sinusitis and bronchitis. On the third day of treatment, she developed nausea, vomiting, fever, sweats, right upper quadrant pain and was found to have an increased ALT to 823 and total bili of 33 micromolar per liter. Viral serologies were negative and ultrasound was reported as unremarkable.

Enzymes normalized after 5 weeks and the narrative does not report anti-smooth muscle antibody.

The first set of labs that were done in this patient reported increased eosinophils by a percentage of 7 percent. Repeated eosinophil counts were not reported. It's probably more accurate to say maybe they were repeated but we didn't see it in our narrative.

The physician who reported this case reported the causation as probable.

Case of interest number 4 is a 44-year-old

female with a history of COPD on a beta-stimulant, budesonide, and corticosteroids. The patient was treated with Ketek for 6 to 7 days for a febrile infection. After 2 to 3 days of treatment she developed severe tiredness, right upper quadrant pain, fever, and icterus.

A follow-up report on March 26th of 2002 clarified no icterus, and the reporter listed with no doubt the diagnosis as "allergic hepatopathy" and Ketek causation as highly probable.

The disorder lasted from February 13th to February 25th of 2002 and resolved 15 days after withdrawal of Ketek.

Transaminases were in the 200 to 300 range. AMA, ANA, and ANCA were reported as negative. We did not see a report of eosinophil count or anti-smooth muscle antibody in our narrative.

The patient was hospitalized from February 13th to February 16th. Serologies for viral etiology were negative, as was for Epstein-Barr. Sonography showed that "there was no congested bile ducts, and the liver was morphological without findings."

A follow-up report the next month in April, April 3rd, the reporting physician changed the cause to idiopathic.

This case of interest number 5 is the final

hepatic case that we just learned about last week, and I'd like to point out that this also is another adverse event that occurred after the reporting period, but since the patient had a fatal adverse event or a fatal course, I should say, we felt it was important to present the case. Obviously, there was a lot going on with this patient. It's quite an unusual case and many confounders exist.

The patient is a 75-year-old male with a history of chronic bronchitis and chronic stable respiratory insufficiency. No history of alcoholism or family history of hepatitis. Concomitant medications include acetaminophen.

Liver function tests were reported as normal 6 months prior to the event. On November 27th, the patient was treated with Ketek for 5 days for AECB exacerbation. He was also treated with prednisolone and increased doses of paracetamol of the maximum dose, 4 grams per day. The patient was also treated with formoterol.

On December 3rd, 2002, the patient experienced fatigue, jaundice, and fever. Lab tests revealed ALT elevation to 2,810 and a total bilirubin of 133. Ultrasound revealed liver normal for size and for contour with homogenous echostructure. No dilatation of intrahepatic or extrahepatic biliary ducts. There was at least one stone in the gallbladder.

During the night of admission, the patient developed a coma and was transferred to the ICU where he was intubated. On December 4th, the next day, the ALT dropped to 595. The patient underwent exploratory laparotomy which did not confirm cholecystis but did show a hard and nodular liver. Postoperatively the patient experienced hemorrhage and multi-organ failure and metabolic acidosis. Total bilirubin increased significantly. Hepatitis A IgM was strongly positive. The patient was also found to have a positive acute serology for Coxiella burnetti.

Measurement of paracetamol 2 days after the admission was low.

The patient died on December 8th. No postmortem was performed as the family refused.

Now I would like to turn to the visual post-marketing adverse events. There were 168 reported visual adverse events from 124 different patients. The most common were vision blurred, visual disturbance, accommodation disorder, and at the bottom you'll see that 36 were reported as serious, 24 not reported with regard to whether they were serious or not, and 108 were reported as not serious.

In the category of visual disturbance, just a sampling of some of the adverse events that were reported

are listed on this slide.

Now, I've selected some narratives to present, and these are verbatim narratives that we received. This first one actually also occurred after the reporting period, but I thought it was important to present. There may be a follow-up on this. The company can let us know about that, but I think thought it was important to present because according to the narrative that we have, the patient had a partial recovery of vision at the time of this report.

It's a 39-year-old woman who received therapy with Ketek from October 25th to 26th for the treatment of sinusitis. There was no mention of relevant history or concomitant medications. On October 25th, the patient experienced vision loss. She had partial recovery of vision by October 29th. The events are ongoing at the time of this report. The reporter assessed the events as highly probably and medically important and serious.

This report came from an internal medicine physician, a report of severe visual disturbance. A 36-year-old female. No information on medical history or concomitant medications was provided. The patient was treated with Ketek orally. The first intake was on October 1st. One hour later the patient developed severe visual disturbance so that she had to rely on her husband's help.

The event resolved after 9 hours and the physician assessed the causal relationship between Ketek and the adverse event as highly probable and considered to be serious.

This report is of a 33-year-old male. It's a spontaneous report. The patient was treated with Ketek from January 13th to January 15th for sinusitis and tracheitis. There's no information on further medications. The patient had no medical history of visual disorders, and on January 15th the patient developed a visual disturbance which was blurred vision affecting near and far sight. He was considerably impaired in his activities. The symptoms started increasingly within hours after intake of Ketek and resolved hours after stop of treatment of Ketek. The end of the event was January 16th.

The patient was not seen by a specialist. According to the physician, there was no alternative explanation for the event. He assessed the causal relationship between the event and Ketek as highly probable and serious.

This case involves a 27-year-old female with the adverse event reported as visual disorder, visual loss. It's a spontaneous report from a physician. The patient received therapy of telithromycin from May 31st until June 2nd. Relevant medical history includes hypothyroidism and

dysrhythmia. Concomitant medications include salbutamol, betamethasone, and thyroxine. On June 2nd, the patient experienced visual disorder with visual loss.

She discontinued treatment with telithromycin and underwent a CT scan and visual field studies. Both were reported to be normal. I just want to point out that this is the narrative, so we don't know when the CT scan and the visual field studies were done with relationship to the actual symptoms.

The patient experienced a complete recovery after discontinuation of the drug. The physician assessed the event as highly probable and serious.

This last case also occurred after the reporting period. These are verbatim excerpts from the narrative.

The adverse event was reported as visual disorder, visual loss. The patient is a 17-year-old female who received Ketek 800 milligrams orally on November 11th of 2002 for the treatment of lung infection. The patient experienced blurred vision 30 minutes after intake of Ketek. The visual loss was a severe blurred vision. It was severe enough to make the patient unable to distinguish her face in a mirror, walk, or eat by herself. It was presumed that the problem was an accommodation problem.

The patient was alone when the event started.

The patient's mother arrived 5 hours later and found the patient in bed due to the event.

The patient has no history of visual abnormalities. She complained of blurred vision in both distance and near vision. The event lasted 12 hours after the Ketek dose was received. The patient was not only unable to read but was also unable to walk due to the visual abnormality. She had to remain in bed and needed assistance with eating.

And that's the end. Thank you.

DR. LEGGETT: Thank you. I think in the interest of time and hunger, we'll take our lunch now. Would the committee members please remember their questions for when we come back? I think we can do the open public hearing. If there is no one to speak, we will then tie in Dr. Rubin's discussion of the pathology and sort of lead on from there and go into the discussion. It's now 1:30. Can we come back here at 2:15?

(Whereupon, at 1:37 p.m., the committee was recessed, to reconvene at 2:15 p.m.)

AFTERNOON SESSION

(2:25 p.m.)

DR. LEGGETT: Hello again. I'd like to reconvene.

Hopefully the way things will go this afternoon, we will have a brief question and answer period for the panel and the FDA, followed by the open public hearing session, followed by Dr. Rubin from Aventis reviewing the liver slides, and then the company talking about those same toxicity data in the post-marketing studies that we talked about, and then hopefully segue from that into the discussion session. And we'll be out of here by tomorrow I'm sure.

(Laughter.)

DR. LEGGETT: Does anyone have any questions for the FDA discussion? Dave?

DR. BELL: Yes. I'm relatively new on the committee, and I would appreciate it if somebody from the FDA could provide some perspective here, as far as they could, in terms of previous decisions when drugs were submitted for approval and had this amount of information and this amount of toxicity information. What has the FDA decided? What have previous committees decided?

I mean, I can form my impression here as to what I think, but I don't know the questions you're asking

us, should this be, should it not be. Is there some perspective?

DR. LEGGETT: Mark or Janice, could you give us a little bit of institutional memory?

DR. SORETH: I can try. In terms of previous advisory committee meetings that have discussed this amount of data that you refer to, I think the experience we have here is unique in that I can't recall the last time we had an application pending where there was a million or a million-and-a-half exposures elsewhere. Can you, Mark? This is a first for me in that sense, in the amount of data.

DR. GOLDBERGER: Yes, I would agree. Certainly the things over the years that I've been involved in, we have not had this degree of post-marketing data. I'm thinking about one of the fluoroquinolones we may have had some post-marketing data but not at the level, for instance, of this.

In fact, we will occasionally have larger sets of data in certain circumstances from treatment INDs that have been in place, most notably I think for some products for HIV while they're in the late stages of development, and that can amount, again, to some thousands of patients. That, of course, can give you a broader picture of safety, but in the setting a drug for HIV, when one is thinking

about the potential benefits versus the safety, there is a different calculus than a drug for the type of indications for which Aventis is currently seeking approval.

So I think there is some level, at least certainly in the anti-infective world, of uniqueness here. I don't know how much of a problem that should really pose. I think it's always hard when you see this amount of post-marketing data to then understand, well, what do these events mean. You can get an idea, for instance, of the extreme level, for instance, potentially of the visual events. I think it's quite clear they have the potential to be very serious. It doesn't mean, however, that they're necessarily that common. We can't really make any estimate.

All we know is that somewhere on the order of a million people got the drug, maybe a little more. Although when the cutoff was for reporting and how much drug actually had been administered may not be entirely clear, the drug was administered in a number of countries whose reporting of adverse events may be very different. You notice, for instance, that all the hepatic events came from Germany, even though, my understanding is, maybe half or less of all the exposures were in Germany, giving you some idea of some of these differences. So we have no sense of what the frequency is. All we know, I think, for the

visual is perhaps what the more severe end may look like. The hepatic I think is quite tricky.

As you know, we have two consultants here, one of whom has already presented, the other is Dr. William Lee. The company has their own experts as well. I was sort of hoping that, as part of afternoon session, we could ask the consultants from both the FDA and from the firm to try to synthesize the information we have about the liver. I.e., we have some information in the animals in preclinical data. We have some small studies in older people with some abnormal liver functions. We have the data you've heard presented from the phase III trials. We have the data from the large safety study, and finally we have the data from post-marketing.

I mean, realistically although you can, obviously, think of each piece as an individual component, if you were thinking about it from a model of clinical medicine and were dealing with a difficult case, one of the things you'd be trying to do would be to synthesize all this and seeing, well, what kind of conclusion at this moment in time can you reasonably draw and how can you then link it to the kind of indications the company is seeking. So that's one of the things that I think may potentially be helpful.

As far as the cardiac, there has been a lot of

discussion. There have been a couple of cases which are not easy to really come to a conclusion because they have various confounding factors. I can tell you when we've gone through these same issues with the fluoroquinolones and when we looked at post-marketing data, when you get a million, million-and-a-half people in, you will get a few cases that clearly look like they might be an issue, but most of them are not clear enough that you can say absolutely. So we don't have a real estimate here of the frequency as well.

The experience in general -- and I want to speak very generally -- with noncardiac drugs for issues related to torsades is the products that can be somewhat problematic potentially may have an effect of their own on QT and then they have the drug interactions usually due to one of the cytochrome systems that magnify their levels, et cetera. We can probably have some more discussion from the people here who are more skilled in clinical pharmacology to get a little better handle maybe on the levels of those. But you can see there's perhaps a couple of events, again in a post-marketing period, that reasonably can be thought of probably in the hundreds of thousands of cases, giving you some only vague idea of what the frequency is.

But that's the best we can do. And you guys are sort of stuck, which is why we use advisory committees,

with trying to take that and trying to link it as best you can to the indications that are being sought and recognizing that it will be a while before, for instance, some of these things are clarified. Truthfully only after substantial additional numbers of patients either in this country and/or abroad are exposed to the drug will things perhaps start to become clearer.

The liver, in particular, is very challenging and that's why we're sort of hoping we have the opportunity to have a little discussion and a little attempt at synthesis because one of the things that's always troubling about liver is, in general, there's no really good way to predict who is going to get it and not a whole lot you can put in product labeling.

With the eye, it may be possible, for instance, to warn people. This is possible. At least don't do anything like driving or anything that requires a lot of visual attention after at least you take your first dose or so to see what happens.

There seems to be potentially the slightest suggestion of an exposure-response relationship. You might be able to say something about that for people with renal-hepatic disease or on certain other drugs.

The cardiac, at least, you could presumably put in some boiler plate statements about certain drugs that

might be contraindicated, et cetera, or if you have certain types of cardiac disease, not that in practice that's always that useful since often the person prescribing the drug doesn't have all that information. But it's a start.

The liver is kind of out there a little more and I think that that's the kind of thing we sort of need the maximum amount of advice that we can get, and we have no hesitation, in addition to using our own consultants, about getting the best possible opinion from the consultants that the company has brought.

So that's about the best we can do as sort of a starting point. Whether later on we can come back and revisit this, when we've heard more information, that's certainly a possibility.

DR. LEGGETT: Thank you.

Go ahead.

DR. ELASHOFF: Yes. This question has to do with guidance on the issue of concluding efficacy based solely on equivalence studies with an active comparator. You clearly need a very clear endpoint in these, and to me the definition of clinical cure is a little vague.

Secondly, you need a small enough equivalence level that not only do you exclude possibly important differences, but you establish that it couldn't possibly be as close as the difference between the comparator and

placebo.

And then thirdly, you need solid historical evidence of the efficacy of the comparator because it's very easy to prove that two different things, neither one of which works, are equivalent. Especially this is relevant to me because, of course, I don't have the experience on this committee, but also Dr. Powers made some comments about the bronchitis situation and that perhaps there would be a high proportion of spontaneous recoveries in that group. So as far as I'm concerned, the data that are presented don't have that last piece, which is to establish and to demonstrate that the comparators are, in fact, effective.

DR. LEGGETT: You summed up nicely the last three or four of our meetings.

(Laughter.)

DR. LEGGETT: Dr. Wald.

DR. WALD: Sort of along the same lines, I think one of the reasons that the FDA sent Aventis back was because of the relative paucity of resistant pneumococci. The hope was that we would have more cases. When it comes right down to it, the number of cases is still relatively small, and when you look at the resistant organisms that cause bacteremia, it gets exceedingly small, and actually very little is added to our original database.

So I would bring up the same question about the comparators. So what we see is that in this situation we get 5 of 7 cases cured or 8 of 10 cases cured when we're looking at resistant organisms that cause bacteremia. I think in this case clarithromycin is not the right comparator. I'm wondering how well an excellent drug would do that had a lot of activity against resistant pneumococci. Are there data, say, from the fluoroquinolone submission of bacteremic S. pneumoniae that were highly resistant? What's the best we can expect under these circumstances?

DR. GOLDBERGER: Well, the data, if I can recall it now, from levofloxacin --

DR. LEGGETT: I can give you numbers.

DR. GOLDBERGER: You remember the numbers?

DR. LEGGETT: Community-acquired pneumonia, there were 245 out of 250, for 98 percent efficacy; 15 of 15, 100 percent for penicillin-resistant pneumococcus, of which there were only 6 bacteremias, of which 5 were severe. And it was on that basis that they got the FDA approval for penicillin-resistant pneumococcus. So the numbers here are actually bigger.

DR. GOLDBERGER: I think our underlying approach was the following with Levaquin, and so it would be our approach I think with any drug. The first step is,

particularly if you're dealing with an out-of-class resistance, as we were with Levaquin for penicillin resistance, and we would, for instance, be with this drug for penicillin resistance, first establish that the drug is effective in pneumococcal infection. And we did that with levofloxacin by having like 250 cases or so with close to a 100 percent cure.

Then establish that the drug is effective in severe pneumococcal disease. I think there was a total of something like 55 bacteremic pneumococcal cases with again levofloxacin a 100 percent cure.

Then establish that the drug is effective in the resistant cases. Again, one of the reasons to do that is in theory you need 0 resistant cases because it's out of class. But practically speaking, we have always been concerned that patients who have infections with PRSP, for instance, may be different in other ways, and it would be prudent to establish efficacy in those patients in case they are sicker or otherwise have other comorbidities, et cetera. So we had 15 patients, and again all were cured. And finally, as Dr. Leggett said, a total of 6 bacteremias all were cured.

So that's kind of the approach that we've, overall, used. What we found most comforting, for instance, with regards to levofloxacin was the large body

in pneumococcal infections, including serious disease, and the very high cure rate. So that's kind of the approach that we've sort of used from then on.

DR. LEGGETT: Yes. Go ahead, Dave.

DR. BELL: Since we're on the subject of resistance, I had a comment that I wanted -- actually two --

DR. LEGGETT: We're not in discussion yet. We're in questions for the FDA.

DR. RUPP: I have two questions, one directed to Dr. Rochester. On page 9 of your handout you showed a nice graph of transaminase elevation for both telithromycin and the comparator drug, broken down into levels above the upper limits of normal. Did you do any statistical analysis on that data? Is there a statistically significant trend towards greater transaminase elevation, or is there a statistically significant increase at any of the specific levels?

DR. LEGGETT: He's referring to slide 9.

DR. RUPP: Slide 9. So it's kind of a brief answer. No, if there wasn't. You made the comment that at each level there were increased numbers of patients with elevated transaminases in the telithromycin group compared to the comparators, but I didn't hear of any statistical analysis of that I guess is what I'm asking for. And I'm

not a mathematician, so I'm not sure what would be the most appropriate test. I would leave that up to your discretion.

DR. ROCHESTER: One could have looked at this and done small sample statistics, exact kind of methods looking at chi-squared approaches, for example, which I think I did at some point in terms of exploratory work. It did not show significance, and I didn't expect it to be significant.

DR. RUPP: Okay, thank you.

Then I guess my second question would be to Dr. Alexander or perhaps to the sponsor. Both your analysis of the data as well as the sponsor's seem to indicate about 1 percent of pneumococci are resistant to telithromycin. Do we know anything about those resistance mechanisms?

DR. ALEXANDER: Yes. Actually the sponsor had also provided data on the genotype of the patients, and there was actually a mixture of those who had mef resistance and erm resistance, but I don't have on the top of my head exactly how that breakdown falls out.

DR. RUPP: I guess my question is, are they feeling that there is ribosomal alteration at that second binding site or is there a presumed telithromycin pump? Something different than erm and mef that we already know about.

DR. ALEXANDER: No, I don't think so. The way that the patients, in terms of the drug-resistant Strep. pneumoniae, were categorized were based on, okay, this is the erythromycin resistance and then they did genotyping of those erythromycin-resistant isolates. I'm not sure if there's any more work that's been done microbiologically in terms of looking at telithromycin resistance itself and the mechanisms --

DR. LEGGETT: I'll ask the company to tell us that because they're going to go into that later.

DR. RUPP: I don't think it impacts immediately upon efficacy or safety, but obviously down the road it would be something that's very important.

DR. LEGGETT: Any other questions? Barth?

DR. RELLER: Dr. Cooper, both from your safety presentation and post-marketing, when I listened to your presentation and contrasted it with what was presented earlier by the sponsor, it seemed to me it's almost as if I were hearing two different presentations. So my question is -- and this has to do with both cardiac events, possible probable liver toxicity, as well as visual disturbances -- is it because you are presenting data that are different, because of newer information or additional information, from what the sponsor presented, or is it a difference in interpretation of the same data?

And coming to the direct question, are you in substantial agreement with their conclusions or in substantive disagreement with their conclusions regarding the relative -- whatever it means is another issue, but the relative risk in these three areas?

DR. COOPER: Well, I think the data that I presented is actually extracted from data that the sponsor submitted and contained in summary tables at the end of their ISS, at the end of their report. So I don't think our numbers are necessarily different.

With regard to trying to draw conclusions with regard to the relative toxicity of this drug in the various areas of special interest, that's more difficult to do and I think part of the reason why we're presenting this to you. Of course, with each individual indication, there will be a different risk-benefit analysis based on this data and different conclusions may be drawn from the same safety data but for different indications.

So I don't think our numbers are specifically different. Whether or not our conclusions will be different after this discussion or into the future is hard for me to say at this point.

DR. RELLER: For example, in listening to the visual issues, they were short-lived, not very serious, not such a big problem in listening to the sponsor. But then

when you look at the numbers, .2 percent of patients had discontinuation owing to visual events. There are clearly differences between comparators and the agent, and if you start looking at even the post-marketing, there were only minimal additional exposures, with the largest post-marketing database that we've ever been presented, or something of that ball park. And yet, if you do some quick calculations, you come up with you should have had 3,000 people that discontinued. Even if you take the severe events in .04 percent, you're talking about 1,200 patients with severe visual problems, but yet we don't see it. So it makes me wonder, no matter how big the post-marketing, if things are not getting through -- something is missing here for me.

DR. COOPER: Well, I would sort of reiterate one of the main problems or a potentially big problem with this sort of passive reporting in the post-marketing safety data in that it is well recognized that there is a significant amount of under-reporting that occurs.

There are other things that I can't really explain to you about this post-marketing data. For instance, for the reporting period that we have, which is until October 1st, the country that had the second most prescriptions was Italy, and maybe the company can clarify this. We didn't really have any reports coming out of

Italy. I don't know why exactly that is. I assume that there are differences between different countries in terms of their infrastructure or their accuracy or ability to detect and report post-marketing adverse events.

I don't know if that helps. Maybe the sponsor could --

DR. LEGGETT: They can address that with all the other things they're going to address I think.

Dr. Maxwell.

DR. MAXWELL: Following on the theme of the visual disturbances, if my memory serves me correctly, most of these were seen in women. What I want to know from the agency perspective, have you seen anything like this before reported in any other antibiotic? And if you have, was the presumption that it was probably due to something related to estrogen or not? Just as a reason why women would be more adversely affected than not.

DR. CHAMBERS: Good afternoon. I'm Wiley Chambers. I'm an ophthalmologist. I'm the Deputy Director for the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products at the FDA.

Let's talk a couple minutes about some of the visual things. I'll try and put some of this stuff in perspective.

The visual disturbances have, at best, been

identified or talked about as being a problem with accommodation and it's not just your ability to accommodate, it's the ability to release accommodation, and was probably best seen in one of the focused studies. That means if you're trying to do a task such look at me, look down to your paper, look back at me, when you first do that initial change, you're not going to be able to either read your paper or you're not going to be able to tell it's me. That will last a few seconds for the most part. That's generally what we've seen.

That, if it's never happened to you before, can be very scary and gets reported by different people in different ways. Some people say, oh, I can't see anymore. Some people say, I've lost vision. Some people say, it's blurring.

Not only do you require being able to focus at different points back and forth, but your eyes have to move together. In fact, as you go and read something, you expect your eyes to converge. So there's some muscle balance that goes along with that. And if that gets to be impaired and there is some evidence that that may be also going on -- it may be some of the reason for some of the diplopia reports. Again, you can't see things quite the way you would expect to, and so you get a wide variety of different reports.

For better or worse, we tend to get more reports from women as far as visual events than we do for men for all drugs. You pick it. I don't know of any particular cases where we've had more for men than women with the possible exception of Viagra.

(Laughter.)

DR. CHAMBERS: You knew I had to throw that in somewhere.

(Laughter.)

DR. CHAMBERS: If you take a look at the comparator rates for the anti-infectives, you will see more reports from the women in the comparator rates than you do from the men. It's just a general phenomenon that we tend to see. So it's not particularly unusual to see more reports coming from women than men.

Whether there's also a factor as far as body weight and body mass, along there, I don't know, but I don't have any reason to believe in anything that's going on that it's related to estrogen or any kind of hormonal factors.

As far as whether I've seen a particular event in any product so far to date, I have not. I have not seen something. We certainly have plenty of products that affect accommodation, but not as quickly, a quick change in accommodation, just slowing the accommodation or slowing

the release, I'm not aware of products go and do that.

DR. MAXWELL: Just to follow up on that, Wiley, the Institute of Medicine report released -- I don't know -- maybe about a year ago that sex does matter in the way women absorb or maybe metabolize drugs and things like that is part of the reason why I'm asking because if this is seen almost exclusively from the data that's presented in women, it just makes me wonder, well, is it just perception or there's actually something else that's different. I don't know the answer. I wondered.

DR. CHAMBERS: The cases for the drug in question are not all women. They are mixed, men and women, but there are more women than men. There are plenty of products that I think alter vision and alter things within the visual system that are different between men and women. I don't see any evidence of that occurring here. I am aware of what you're referring to.

DR. LEGGETT: I'd really like to stay away from discussion. I really want questions.

DR. O'FALLON: But they were all so young. I thought that was an interesting thing that the visual disturbances were reported primarily in the young, and I was wondering why.

DR. CHAMBERS: We do know from the higher doses and looking at it, that there's definitely an effect on

ability to accommodate and your ability to release accommodation. For better or worse, everybody in this room starts losing their ability to accommodate at birth. We start with a great deal of reserve. For most people that means they need reading glasses to help with that accommodation at about the age of 40, but you're losing it all the way through along, and those people who are younger have much more accommodation, much more ability to quickly go and look at different things. So any drug that's going to affect that is going to have a much more pronounced effect in the younger than older.

DR. LEGGETT: Barth.

DR. RELLER: Question. Are there other drugs that have a similar magnitude of effect, and if so, some examples so that we have some comparative information of, well, you see this degree of difficulty with accommodation with drug A, B, or C, or you see it with A, but this is an order of magnitude 5 times, 10 times as frequently as that, to get some balance in this?

DR. CHAMBERS: Probably the biggest class of products that affect accommodation are the cholinergics, and things that affect the cholinergic system will affect accommodation. We clearly have products that do much more in magnitude of accommodative retardation than this does. Those products, while they have a bigger magnitude, are not

an on-off kind of phenomenon. They're not a slowing. They impair accommodation. They don't slow your ability to do things. I'm not aware of other products that do exactly this type of thing where they just slow it and/or slow the release. That I'm not aware of other products.

DR. RELLER: So this is real. It's different, and what we have to grapple with is simply the magnitude of the problem relative to the benefits? Would that be a fair summary?

DR. CHAMBERS: Yes. I think it's real. I think it's dose-related which is why in the higher doses you see it. The focused trials on it used 2,400 milligrams and were able to elicit it in up to 50 percent of the people, approximately a third or so, but enough to clearly study it. That's clearly not consistent with the normal reporting, but there is clear reporting. There's a clear difference between comparator groups and this drug. So I don't think there's any question it's the real phenomenon.

The difficulty you have is that different people report things different ways and you get these magnitudes. You know, I completely lost vision to just a mild blurring. And some of those events may be the same events. You're just getting the filter of how people report them.

The difficult issue I think is people are going

to have problems if they have to change focus. If you're trying to drive and you're trying to look at the speedometer and look in the distance, you can't go back and forth and do that quickly. So there are going to clearly be people that are going to be affected in doing that and other tasks that are there. And you need to evaluate how much those kind of activities weigh.

In many cases we have labeled those kinds of products. We've permitted them on the market and labeled them. That is entirely possible to be done with this particular product based on what we know. Whether that's enough is a judgment we're asking you.

DR. LEGGETT: Thank you.

Janice?

DR. SORETH: To try to answer a specific question that Dr. Maxwell raised which was do we see this with other antibiotics, I think to date we have not with other antibiotics that I'm aware of. However, recent experience with fluoroconazole led to labeling that anti-fungal for patients with candidiasis, candidemia -- Aspergillus, I'm sorry -- because up to 30 percent of patients reported visual problems. Now that's in a setting of a parenteral drug where patients by and large are hospitalized and have a serious infection, life-threatening in cases.

So I think you have to temper what you see, take it in balance with the formulation of the drug, in this case oral, treating outpatients with respiratory diseases that span a spectrum from pneumonia to sinusitis to bronchitis who will not be hospitalized, who will be, by and large, out and about and take into account how a visual disturbance that might last minutes or can be reported to last hours spans the spectrum, how that might affect their day-to-day activities.

I think one thing that looks different from the clinical trial reports, AE reports, versus what we have post-marketing seems to be differences of degree. We didn't get the more alarming kind of reports reported by patients in terms of I couldn't see my face in a mirror, had to lie in bed until the mother came home. That sort of thing wasn't seen in the clinical trial database, but post-marketing, we have seen those kinds of reports.

Again, numerator and denominator. I don't have a good handle on that. I don't know the precise number of cases, for example, coming from Germany with regard to reports of visual adverse events and the exposures there which are not a million but maybe, as of October, 500,000.

DR. LEGGETT: As a follow-up to that, Dr. Cooper, in your slide number 24 where you talked about phase III trials with 50 percent of AEs and then 3014 with

23 percent and you sort of shrugged your shoulders, is that because you really have no idea or does this happen a lot from one study to the next? Or actually that's Dr. Rochester. Sorry.

DR. ROCHESTER: I'm surprised that I did shrug my shoulders.

(Laughter.)

DR. ROCHESTER: But no. The thing is when you look at safety data in its complexity and entirety, one has some general expectation for adverse events rates overall, and from drug to drug and study to study and so on, there's always going to be some variability.

But if we look at, say, telithromycin studies -- there were probably 17 or so phase III trials -- within those trials you would see a certain rate, variable but within the 40 percent, let's say, 50 percent range of adverse events and some of them certainly without causality being attributed to drug. We're just saying this is what we see.

And then if you enrich a specific safety study in which you enriched the population in terms of comorbid conditions and improve their numbers of subjects that are exposed to concomitant drugs and you're studying the same sort of infections, even though to enroll in the trial you didn't have that strict criteria that we use in the

efficacy, but we're trusting that if a physician says you have pneumonia or you have sinusitis, that's what you have basically, and if you get into that trial and you have this mixture of things that would say up and above your regular situation, you should enrich for more AEs, then I would expect the AEs to be somewhat closer to the trials.

What I'm seeing is about half as many, and then trying to think as to possibly why -- I realize in the original studies half the patients were CAP patients. They seemed to have had more such events. And in designing this new trial our goal was to certainly see more of the safety profile in CAP patients. But we set a target of 40 percent CAP or AECB. Well, it turned out we do have our 40 percent, but the composition of that 40 percent is 10 percent CAP and 30 percent of AECB.

Then I also thought it could be related to just probably a fairly much healthier population. That's possible, but I still don't feel very reassured in the sense that the comorbid conditions were there. The concomitant drug use was there. Several other factors actually made both arms look quite similar in every subgroup that I looked at. So I would have expected more. Exactly how much I would have expected I don't know, but if I saw something like 35-40 percent, I would have felt better about the vigilance probably in which these adverse

events were collected.

DR. LEGGETT: Thank you.

Dr. Goldberger.

DR. GOLDBERGER: Just to follow up on that in terms of a potential explanation, over the years in different settings, we have used sometimes in the treatment IND format, sometimes without a formal treatment IND, large open-label studies far along in development programs while the product is being reviewed, et cetera. And there is data collection with regards to safety, but one of the observations realistically is that the quality of the follow-up, the quality of data collection in these studies is just not at the level that it is in randomized trials, even if these big studies are in fact randomized. It's just not the same level. So one of the things we've observed is in these studies adverse event rates tend often to be lower.

But what you do get, however, is by enhancing your denominator substantially, you do get the opportunity to see some patients who may have these concomitant factors where a rare or unusual adverse event will show up, which can be quite helpful in rounding out the safety profile. So you get the more common events clearly defined in a randomized trial. Sometimes you get the less common events, you get a clue to them by these larger trials, and

then you sort of have to put the whole thing together.

It's one of the reasons on occasion we will discourage sponsors who like to take all the studies together, these large studies and their controlled clinical trials, average out the adverse event rates and then put a single number in the label. Often it's better to provide the information separately since it gives a better picture.

DR. ROCHESTER: Shall I just add one sentence here too?

DR. LEGGETT: If it's only one sentence.

DR. ROCHESTER: Sure. In addition, though, the only difference or reassurance in here was that the types of adverse events, if you look at the system organ classes, gastrointestinal, nervous system, whatever, remain consistent with the phase III trials.

DR. LEGGETT: Okay.

Dr. Wald.

DR. WALD: Dr. Cooper, you presented five cases of interest in terms of the hepatic toxicity. Did you make a best estimate for each of those cases as to whether or not there was an association with the drug? Because you didn't tell us that.

DR. COOPER: Well, I think because of incomplete information, it's difficult necessarily for me to draw a conclusion based on those cases. I think the

cases where there's a liver biopsy provide us with an opportunity to explore a possible connection in more depth and maybe perhaps more accurately. I can't say for sure. I think that there's information missing from all of those studies. That makes it difficult, but I think that the biopsy cases might be helpful.

DR. LEGGETT: I think, Ellen, we're going to ask the four consultants to give us their views.

Since there are no more questions, I won't recognize any more questions.

(Laughter.)

DR. LEGGETT: Why don't we pass on to the open public hearing. We did not get any requests. Are there any requests from people here? Seeing none, I would like to pass on to -- oh, is there one? I can't see an arm. Yes, go ahead. State your name and also please disclose any financial potential conflicts of interest.

DR. BROOK: No financial conflicts. I'm Itzhak Brook from Georgetown.

Just a short comment, since nobody mentioned it, that there is a situation where resistance to a macrolide may clinically be important and that is in the penicillin-allergic patients where there's no other choice.

DR. LEGGETT: Thank you.

Could we have Dr. Rubin come and give us your

hepatic pathology interpretation?

DR. RUBIN: Good afternoon. I'm Emanuel Rubin. I'm Chairman of the Department of Pathology at Thomas Jefferson University Medical School in Philadelphia. Just briefly, I have had a longstanding interest in liver disease and I have been examining liver biopsies for some 40 years, going into the many thousands.

I had the opportunity to look at the slides of the patient from Finland who had two biopsies that was shown here previously and also the gentleman who had a gallbladder condition and who also had some cholestasis.

After I looked at the glass slides through the microscope, they were also examined by other members of the liver panel here who I think by any standards are nationally recognized experts in liver disease: Drs. Maddrey, Sorrell, Young, Watkins. And what I'm going to indicate to you is really a unanimous opinion and our consensus.

When you look at slides, it's like looking at a photograph of, say, a face and, say, two women, presented with the same photograph of a man's face, one might say he's very handsome; the other would say, well, he's interesting.

(Laughter.)

DR. RUBIN: So I want to congratulate Dr.

Kleiner for a scholarly discussion, and actually I think we're in agreement on most aspects. I, together with the other members of the panel, would differ perhaps on some emphasis, but he has a sharp pathologic eye.

So let's go to LB-3. This is the 72-year-old man who was treated with the drug and who had chronic cholecystitis, among other things, and cholelithiasis. As you can see, there is some change at this low power view. It doesn't tell you all that much.

Now, LB-7 please. Now, here what you can see here, this is a hemotox. It's not connective tissue. But here's a scar and this is fibrosis. Here's a portal tract going the entire width of the biopsy here, and then another spur of fibrous tissue here going this way. It's like a Y. And this is old fibrosis. There are very few inflammatory cells here. The collagen is clearly old. What this tells us is that there has been some chronic condition here, perhaps repeated episodes of cholangitis. This is a gentleman who had stones and I believe was probably passing stones, perhaps some silent. He did have some abdominal pain, some were symptomatic. In any event, when a stone enters the common duct, it is very common to get an ascending infection, ascending cholangitis.

Now, LB-4 please. Now, we can see that this man does, indeed, have changes consistent with an ascending

cholangitis because this is a portal tract and you see that the portal tract is infiltrated not only by chronic inflammatory cells but by a few acute inflammatory cells. So this is a mild ascending cholangitis which reflects the passage of gallstones down the common bile duct.

Now, let's have number LB-5. Now, here is a high power of the liver. You see most of the liver is actually bland. There's very little going on here and you can see one brownish area there. That really is the extent of cholestasis. Occasionally you see these small bile passages that contain dried or inspissated bile. So he does have a cholestasis which is consistent with stones and an ascending cholangitis and other evidence, clinical and structural evidence, that all of this reflects chronic cholecystitis and cholelithiasis.

Now, Dr. Kleiner did mention that this was certainly a strong possibility, and I agree with him. My emphasis would be that this is the diagnosis.

Now, we then come to the other case which has elicited a great deal of interest and was discussed previously, that of the man who had two biopsies and autoimmune hepatitis. I'd like to go through the second biopsy first just because we're quite clear as to what that biopsy reveals.

Let's have LB-16. Here's a connective tissue

stain of a biopsy. This is a needle core biopsy. The one thing you can see, as Dr. Kleiner pointed out, there's a lot of collagen, a lot of scarring -- collagen means scars -- a lot of scarring in this liver which is in almost every lobule and actually beginning to surround nodules of liver tissue. Now, we call that, when it completely surrounds nodules of liver tissue, cirrhosis. This is not a full-blown cirrhosis but it's on the way. This is an early cirrhosis.

Now, LB-17 please. Now, if we look at a higher power in the liver, we see there are inflammatory cells all over the place and they look like so-called lymphoplasmahistiocytic, which means there are chronic inflammatory here, lymphocytes, plasma cells. There's dropout of liver cells here. This is a classic appearance of autoimmune hepatitis.

And if we'll go to LB-18 please. Here under higher power you can see what these cells look like. There are certainly no eosinophils. There is not a true zonal distribution. They are scattered throughout the parenchyma, and the interface between the collagen and the parenchyma of the liver is an irregular, so-called piecemeal necrosis. This is the classic appearance of autoimmune hepatitis with early cirrhosis. So it's been going on for some time. You cannot get this appearance in

a day or a week or a month. This is a chronic process that's been going on for some time.

And Dr. Kleiner again I believe favored autoimmune hepatitis. Dr. Goodman from the Armed Forces Institute of Pathology favored autoimmune hepatitis, and considering the fact that he had anti-smooth muscle antibodies in very high titer, which is an autoimmune phenomenon, I think we can safely diagnose this as chronic autoimmune hepatitis with early cirrhosis.

But now that we know all of this, we know this man's chronic course and what the underlying disease is, we can now go back, because we now have more information, to the first biopsy and take a look at what that is.

The first biopsy, if you'll remember, was in a man who had elevated transaminase before he received the drug, before he received the antibiotic, which tells us that he has a preexisting and continuing liver disease before he ever got the drug. He also had a peripheral eosinophilia which is characteristic of many types of allergic asthma. He also had an episode of some gastrointestinal infection which apparently was in the family. We don't know the nature of it, but remember that the products of infection in the gastrointestinal tract go into the portal vein and are then carried throughout the liver. So a reactive hepatitis -- we don't ordinarily

biopsy for that, but a reactive hepatitis to gastrointestinal infections is actually very common in biopsies that are taken incidentally for other purposes.

In any event, let's look at LB-9. We don't see much. This is a low power.

And go to LB-10. Here we see a little bit of fat. That has no meaning. This man is a diabetic. A little bit of fat in the liver in a diabetic doesn't really tell us much.

And let's go to higher power right away, LB-11. Now, here we see a liver which is certainly distorted by the presence of numerous inflammatory cells. Here Dr. Kleiner and I and our panel would differ in the emphasis. There is definitely some accumulation of inflammatory cells around central veins, but they also can be seen in the vicinity of portal tracts. There are two small bile ducts over here. There's one there. That's a small bile duct, and the other one doesn't show up well. And there are some eosinophils in here.

Now, the presence of eosinophils in a person with peripheral eosinophilia and who is hyper-reactive for eosinophils, as allergic asthma is, such people will get eosinophils in virtually any inflammatory reaction in the body. The liver is not an exception and the eosinophils in this case simply are a background phenomenon. The

important cells here are the lymphocytes and the plasma cells, of which there are many.

Next please, and here under higher power you can see that there is liver cell dropout. There is not what we call true zonal necrosis. We call it coagulative necrosis or eosinophilic necrosis. Most of these cells are actually -- the background cells are macrophages here and those macrophages have been there for some time. They're the cells that come late in the inflammatory reaction, tend to mop things up, are not characteristic of drugs, but are characteristic of longstanding chronic inflammation in the liver.

The next is LB-14.

DR. LEGGETT: How many more of these are we going to go through? This is almost discussion. I'd rather save this.

DR. RUBIN: All right. That's enough.

So what we have basically is a liver that has many macrophages, these late-appearing cells, with a background of eosinophils which is accounted for by the allergic asthma and the reactivity, the peripheral eosinophilia. And knowing now what the underlying disease is, this most likely represents a flare of autoimmune hepatitis, which again Dr. Kleiner alluded to as a possibility. I would put that certainly as the most likely

diagnosis here.

DR. LEGGETT: Thank you.

Dr. Caffe, could we go on to the responses that we carried over from this morning real quickly? Or Dr. Leroy, whoever.

DR. LEROY: Yes. So one of the questions was were CPK drawn in patients taking statins, and the answer is no in this usual care setting. But Dr. Lagarenne emphasized that there was no myositis in those patients.

The second question was did we try to see, in patients who had blurred vision, if they were taking this drug before bedtime, they would experience the blurred vision. We did not perform such a study, but as explained also by Dr. Lagarenne, when we've been able to measure accurately the duration of the symptoms, it was with a median time of 2 hours. The long duration is more because of the collection of the adverse event in phase III that are reported in an adverse event form. But when we've been able to precisely investigate the duration, it's largely within 12 hours. So it could be one other possibility.

DR. LEGGETT: I was also referring to, though, you were going to collect some data from the leftover questions from this morning.

DR. LEROY: Yes. Those data have been provided, if I can have those data.

DR. ELASHOFF: Do you want me to just provide it?

DR. LEGGETT: Yes.

DR. ELASHOFF: Basically they gave me mean date on which cure was evaluated and the standard deviation, and the range for each of the CAP studies and the bronchitis studies and the sinusitis studies. The means appear generally to be very close. If there's any difference at all, the comparator is slightly larger by .1 of a day. The ranges are sometimes extremely large, as in one case where the range of the day on which cure was established was 4 to 35. In one or two cases, it's really as low as 17 to 23 as advertised, but there isn't any real evidence of systematic difference.

DR. LEGGETT: Was there any other question left over from this morning? Does anybody remember that they had a question?

DR. PATTERSON: I think someone asked about the susceptibility of the Staph. aureus superinfection.

DR. LEROY: I think it was answered. In sinusitis, they were all susceptible to telithromycin, and Dr. Jenkins provided an answer regarding the susceptibility depending on the susceptibility to erythromycin.

DR. PATTERSON: No. The superinfection that occurred. Somebody asked about the Staph. aureus

superinfection that occurred.

DR. LEGGETT: The one in the urine.

DR. LEROY: In urine, yes. No, we do not have the MIC to this Staphylococcus aureus. But this is the narrative of the patient. I think that we need to go quickly through this patient because we've already discussed this patient.

The patient had Streptococcus pneumoniae resistant to erythromycin with the genotype ermB and MIC to telithromycin at 0.03, had an initial improvement, sterilization of blood culture at day 12 and secondary -- no, in fact on therapy, and at day 12 of therapy, he had a recurrence of dyspnea and fever and a secondary UTI infection, Staph. aureus, which was treated with intravenous antibiotic.

DR. LEGGETT: Thank you very much.

DR. LEROY: Thank you.

DR. LEGGETT: I think I'd like to pass on to the discussion. Unless there are any other questions or any other problems, what I would like to do is perhaps talk through the safety issues so we get everybody's opinion or discuss those, go to the efficacy issues, and then pass on to the answering of the questions.

DR. LEROY: Would it be just possible to provide some clarification regarding the case reported as

torsades de pointes, or will we have time to clarify just this case and the ECG reading of this case?

DR. LEGGETT: Can we do that later as it comes up in the safety issues?

DR. LEROY: Fine.

DR. LEGGETT: David.

DR. BELL: Well, my comments about the public health issues don't fit neatly into either efficacy or safety. So do you want me to hold them?

DR. LEGGETT: Yes. That will go with that discussion, after the safety, go to the efficacy. That will be part of that.

We have heard varying discussions about the etiology of the hepatic injuries on the side of Aventis and of the presenter, Dr. Kleiner. Dr. Goldberger, you said there was another expert?

DR. GOLDBERGER: Yes. We would like Dr. William Lee, who we invited here.

DR. LEGGETT: Okay. I didn't know if that was someone in addition to Dr. Lee.

DR. GOLDBERGER: No. There's Dr. Lee and actually perhaps if you might ask Dr. Kleiner to respond to some of the comments that were just made by one of the Aventis experts, we'd be very interested in hearing that as well.

DR. LEGGETT: That would be great. And then what I would like to have Dr. Lee start off with is his take on this as well. Dr. Kleiner, do you want to go first?

DR. KLEINER: Sure. I agree, as Dr. Rubin said, with many of the things that he said. I think I would still stand by my own interpretation of the features that I saw. I do think that there was more definite evidence of injury in zone 3 in the first biopsy, and I think of the three, that's certainly the most suspicious for involvement of drug. I think it's entirely reasonable that the patient may have had an underlying autoimmune hepatitis the whole time, but that doesn't mean that you can't have a superimposed injury by something else. Patients have two diseases all of the time. So I do think that that's possible. It may have exacerbated an underlying condition, but I think that there is evidence for separate injury.

As to the other case, it could go either way. I think there is so much overlap in the potential patterns of injury from a drug and from acute large duct obstruction that I interpreted the fibrosis as possibly related to the patient's diabetes. Diabetics are known to get sinusoidal fibrosis. That can be present without any of the other features of standard hepatitis.

I think we're in substantial agreement on what was seen. It's our interpretations that vary a bit.

DR. LEGGETT: Dr. Lee.

DR. LEE: Yes. I think this is quite a unique situation for consideration of hepatotoxicity in part because this is a drug that would be used widely and would be used for short periods of time, 5 to 10 days, and for the most part, I guess 5 days in duration. Now, while that, on the one hand, gives you less exposure and we know that drug reactions often take more than 5 days and certainly more than 10 or 20 days in many instances, so the good side would be that the shorter exposure means you probably will have less toxicity. The other side of it is that you may have toxicity that shows up after the drug has been discontinued. Indeed, that appears to what has been seen in a couple of cases.

Now, I think there are probably some signals for hepatotoxicity here that are real. I think there were certainly signals in the animal data. There were signals in the high dose data in the elderly in the phase I. Even if you throw out a good percentage of the cases, which are always confounding in the clinical studies and certainly in the post-marketing studies, there's probably still a few real cases in here.

Again, I think the issues for us as the

committee would be to consider whether people are going to use this drug outside packaged labeling. And certainly this has been partially addressed by the sponsor. There will be people who will be taking repeated courses of medication in the future. Now, I would take it that there would not be too many instances where one would be likely to take prolonged courses like, say, 3 or 4 weeks, of medication.

I think it's unlikely that there's zero toxicity with this drug. I think the antibiotics as a class are right up there with the nonsteroidals as likely drugs to have hepatotoxicity.

I think the amount of data that we've been shown has been very exciting. It's really a new benchmark for other companies coming to FDA to have 12,000 patients exposed in this most recent study and to have this much post-marketing data as well. And we haven't seen a case of acute liver failure although, as we know, post-marketing data is notoriously unreliable in this country, so I doubt that it's any better over there. I think the point about the Italians not having any cases show up is simply they didn't show up. At least it appears not.

Now, as far as this one case that everyone has beaten to death, the poor Finnish man, I still would interpret it differently than Dr. Rubin and the expert

panel and say that this looked like a drug hepatotoxicity case. I reviewed the slides at lunchtime. I don't know what else to say. It's loaded with eosinophils. I don't see why they can't be there due to a drug reaction, but I take the point about the possibility that he certainly was an allergic person to begin with.

The time delay to having hepatotoxicity looked very good. He didn't have cirrhosis at that time, and then a year or a year-and-a-half later, whenever he had the second biopsy, he's evolved to something. And I still would posit that it's theoretically possible that the drug triggers something that becomes an autoimmune hepatitis. There wasn't a lot of evidence for autoimmune hepatitis on the first biopsy. But again, we can differ over that one.

I think the second case, the 72-year-old, was a cholecystitis case and we should just drop that. I don't think it's very likely. I think the amount of damage was very minimal although the biopsy was quite late.

So to sum up, I think there's really been a lot of data presented. I think again there's been no bigger study than the 3014 study that I'm aware of. However, the data suggests that there may be some people who have LFT abnormalities that are seen late in a very small percentage. Although, again, if they're only going to use it for 5 days, it's not going to appear.

But I guess the question that we still don't have an answer to is whether a year or two later, when they get the second course, they would have an accelerated reaction. The model for that, of course, is halothane where it was multiple exposures associated with eosinophilia, associated with fever, with shorter latency with each secondary exposure. Now, I don't know that this is anything like that. I'm not saying that, but I'm saying at least that model is there.

The other model, of course, for length of treatment would be the analogy to bromfenac where again the agency said this was for limited use, only 10 days, but since it was a pain reliever, it was used for longer periods of time and the toxicity first appeared in patients who had been taking it more than 30 days. Again, I don't think that really applies here either because I think it's only going to be used for 5 days presumably or maybe 10.

So I think overall I think the sponsor said it right. The toxicity is going to be there and it's going be in the range of other antibiotics. I don't think it's zero and I don't think it's in the range of isoniazid. I think it's likely to only be fully measured once the drug is approved.

DR. LEGGETT: Thank you.

Alan, did you want to have a question?

DR. CROSS: I wonder if I could ask the hepatic pathologists a general question. I was struck by the inconsistent patterns from patient to patient here, and is it reasonable to suggest that before we associate a specific drug with hepatic toxicity, are we looking for similar types of injury patterns? Or are we just simply trying to differentiate between chronic and acute damage? Or is there a whole panoply of changes which can be associated with antibiotics that have come to be associated with hepatotoxicity?

DR. KLEINER: Well, first of all, drugs have been able to mimic everything in liver disease that's not caused by a drug. So you can get any pattern of injury from a drug that you can get from something else.

The problem with cases like this is that we're really sort of operating in an information vacuum. We don't know what pattern of injury to look for because there really isn't any precedent with this drug. All we have are the three liver biopsies that we have, and they all show different things. So you have to sort it out in other ways. If, as it turns out, one is just acute large duct obstruction, has no relationship to a drug, and the second biopsy on the Finnish patient turns out to be a chronic thing that's related or unrelated to the initial episode, you might only have one pattern. Or if one makes the

argument that none of these are related to drug, well, then you haven't got any pattern yet at all, and all you have are the other evidences of hepatotoxicity that are based on clinical laboratory values and follow-up and things like that.

DR. CROSS: But based on a drug, for example, like INH, where we tend to see a highly repetitive, similar pattern in that instance where we've already made the association between INH and hepatotoxicity, would we see a similar biopsy pattern?

DR. KLEINER: Yes, in general, although some drugs do have more than one injury pattern. Generally speaking, the same drug will result in a similar -- but it can still have a broad spectrum just like chronic hepatitis C can be very mild or very severe.

DR. LEGGETT: Any other questions about hepatic toxicity? Barth.

DR. RELLER: Dr. Kleiner, you said there may be few, maybe no pattern associated. Is there any help? I was noticing the earlier information not presented today when this drug was discussed before, the statement that hepatotoxicity was seen in all species tested. These were dogs, rats, and monkeys. So were there any patterns there or does drug toxicity in animals look totally different from drug toxicity in humans? I mean, are we totally

without any leads is what I'm asking.

DR. KLEINER: Sometimes you can get some information, but animals can be very different from humans as well. I didn't see those slides, so I wouldn't have been able to compare them anyway. It's, I think, helpful if you understand what the mechanism of injury is and to know how related it is to the species. And if you saw the same injury pattern across many, many species, then that's probably good evidence.

Somebody has something to say.

DR. LEGGETT: Please enlighten us.

DR. PETERS: I'm Terry Peters. I was the original reviewer for this product, and I'm an acting team leader in the Division of Anti-Infective Drug Products.

The things that I can tell you about this drug from an animal perspective is that the liver function tests in these animals were quite markedly increased. I can tell you that phospholipidosis, which is a not uncommon finding with some of the macrolide antimicrobials, indeed was significant with this product. I can tell you that we had some increases in bilirubins in basically all species. We had more significant liver effects in rats than in dogs with necrosis and fairly significant effects. Can I give you comparators? I can tell you that the signal was fairly strong which is why all the emphasis, when we got into the

clinical trials, to evaluate the hepatic effects.

DR. LEGGETT: Jan.

DR. PATTERSON: Would we expect this hepatotoxicity to be more common in people with underlying liver disease, or is it totally idiosyncratic?

DR. LEE: Most times there's not a good correlation between presence of underlying liver disease and increased susceptibility. Now, there may be some in certain instances like veno-occlusive disease, but for the most part, as I think the data showed, there didn't seem to be any tie-in to increased toxicity in people who had preexisting liver disease. Now, you might not want to get two diseases at once, but there doesn't seem to be increased susceptibility.

DR. LEGGETT: Dr. Lee, a comment. We in infectious diseases are really used to seeing hepatotoxicity with antibiotics, and I think it's seen a lot more. What's your gestalt on the hepatotoxicity with telithromycin? Is it in the ball park of several others, or is this 2 standard deviations above or what?

DR. LEE: You're saying clarithromycin versus --

DR. LEGGETT: Yes, or Augmentin or erythromycin estolate or rifampin.

DR. LEE: Yes, I think this is in the ball park

probably of Augmentin or erythromycin perhaps. Now, Augmentin is more cholestatic, but again, it's often used for longer periods of time as well.

DR. LEGGETT: I'm just waiting for this drug to be used for 4 months for disseminated Mycobacterium and then we'll really know.

(Laughter.)

DR. LEGGETT: We've beaten hepatotoxicity to death I think.

Why don't we pass on to visual since we still, hopefully, have our ophthalmologist here. Any questions or further debate on the part of the members here about the visual toxicity question?

(No response.)

DR. LEGGETT: Okay, everybody wants to go.

How about the final one on the cardiotoxicity issue? Dr. Leroy, if you or someone could --

DR. LEROY: Yes, thank you. I would like to call on Dr. Pratt to comment on this case that was reported as a torsades de pointes.

DR. PRATT: Good afternoon. You've had a little bit of a tough time today. You have multiple, different issues to consider and I know that torsades de pointes VT isn't on the tip of all of your tongues.

I'm Craig Pratt. I'm a professor of medicine

at Baylor College of Medicine. I've been former chairman and long-time member of the Cardio-Renal Advisory Board that we affectionately call CRAB.

(Laughter.)

DR. PRATT: My research interest is in arrhythmias, sudden cardiac death, torsades. I've had the opportunity to chair the cardiac events committee of 3014 which even in cardio-renal we'd be pretty proud of in terms of the size and the substance the study.

My overall view of teli in the big spectrum of noncardiac drugs causing torsades is that the risk is very low, and I'd be happy to tell you in a couple of sentences, but let me, since I was asked to talk about this report, talk about it first.

Now, those of us that have worked on advisory boards like cardio-renal really take these reports seriously, just like the agency does. But while we take them seriously, I think that a previous President said it best. He said, trust yet verify. So why don't we verify what we know about the case, if you could project CK-26 up there.

First of all, if we look at the risk of sudden cardiac death in general, this would have been a posterman for the issue. He was a middle-aged, white male who was quite heavy who had heart failure, angina, previous

angioplasties, multiple risk factors for cardiac disease, and most members of his previous family had already dropped dead. So it's a little bit of a shame he didn't have a real workup in a real medical center.

CK-27 please. If we look 3 days prior to any treatment with the present subject telithromycin, he had a syncopal episode. So whatever was going on with him was already going on. At a time that he was evaluated after a motor vehicle accident 3 days ago for another syncopal episode, he had a normal QT interval.

Then on the day of his death, we actually have some rhythm strips which Dr. Cooper has shown you, and I would like to review. CK-28.

To do this, what I'd like to do is just remind you that from a cardiologist perspective, especially those in arrhythmias like myself, torsades means something very specific. It's pause-dependent, polymorphic VT with QT prolongation. And I think that Dr. Soreth started the day, a long time ago now, with a quote from Jeremy Ruskin who was one of my co-people on the CEC of this project, saying that it's really the drugs that not only prolong QT a little bit, but that with a combination of comorbidities and co-therapies can lead to great accumulation and rapid and great increases in QTc interval. So let's reflect on that when we look at this patient.

This is a patient who has a normal QT interval. There it is right there. It's about even corrected, about 420 milliseconds. This is some noise over here. Dr. Cooper presented one other strip that I didn't have, but it would have been great one for my cardiology fellows because it was full of artifact. CK-29 then shows us what happens. Within 30 minutes of having a totally normal QT interval, this is just, of course, ventricular fibrillation, exactly the kind of arrhythmia that occurs in obese patients with a family history of everybody dropping dead, coronary artery disease, status post-myocardial infarction.

And CK-30 is simply a more agonal rhythm 9 minutes later.

So if we take pause dependence, we take polymorphic VT with a torsades look, and QT prolongation, the three components of torsades, we have none of them. The reason we are so specific is if we identify something that's pause-dependent with polymorphic VT and QT prolongation, it almost invariably really is drug-related. So this case doesn't meet that criteria.

If I just take one more minute, I'd just like to make a couple of points of why I think that on the spectrum of noncardiac drugs, this is a relatively low risk drug. And to do that, I'm going to shorten what I told my group, so I'll drive them totally crazy and go directly to

CK-12. We made CK "cardiac kit." That's quite cute. So, CK-12. If you put that up there.

You saw this before, but from the standpoint of clinical cardiology, I think this is very important. Remember we said the outliers that have comorbidities like heart failure and might be female and might be elderly, all high risk for torsades, who were on CYP 450 drugs and all sorts of other things, would have high plasma concentrations. These are the plasma concentrations that exceed the normal for teli by 3- to 7-fold I guess. And if we look at the EKGs within 30 minutes of those numbers, we have no QT even reaching 440. So this tells me that when we talked about the slope -- and you were already given the formula for how this was figured out -- that's a lot of fancy talk, but the bottom line is that even high blood concentrations did not lead to a QT interval that was near what we get concerned about for the risk of torsades which is a cutoff that has proven through history to be pretty good, 500 milliseconds.

And if I could just go to one other thing, number 13. If we look at this, I just want to point out that we have a lot more information here because in addition to QT, which can drive you crazy if you just keep listening to it, we have a lot of information about comorbidities and co-therapies. And to just remind you,

16. CK-16 up please.

We had 5,000 patients over the age of 65. A lot of them were females who could have a 2- to 4-fold increased risk of torsades. A lot of patients even above the age of 75, and on CK-17, if I could have it up please, not only did we have 4,500 patients on CYP 450 3A4 inhibitors, but over 11,000 on CYP 450 substrates. So this is a big database with no signal, and I think if we look at the preponderance of the evidence with this drug, we would conclude that the risk is very low for torsades.

Thank you.

DR. LEGGETT: Thank you.

David, could you talk to us a little bit about the public health thing? Because in terms of toxicity data, to me the question of vasculitis or not vasculitis is such a rare event. It's probably the same idiosyncratic thing as we have with other antibiotics. Unless somebody has something different, another thought about that. I mentioned the vasculitis because it was on one of the first slides this morning.

DR. BELL: Thanks. I wanted to make a couple of comments on the public health issues. These are stimulated in part by the discussion that John Powers so nicely had this morning about public health impacts of macrolide-resistant Strep. pneumoniae.

The public health impact of drug-resistant infections can be difficult to define, particularly when the infections are not life-threatening and other drugs are available to treat them. Even when they are life-threatening, there are often comorbidities. So to do the necessary studies to really define the impacts can be resource intensive. Those resources have to be devoted from other public health priorities, and sometimes there's a delay in getting that done.

Partly for that reason, we are sensitive to other parameters, including upward trends in resistance rates and anecdotal reports of treatment failures that accompany these upward trends. We frequently use this information to identify a public health hazard and to take action partly because of the difficulties involved in defining the impact, but also if we wait until there is a conclusive public health impact, the chances are that resistance has reached such a high level that it's too late to save the drug so that any preventive interventions at that point are too late.

When I talk about saving the drug here, I'm talking about saving macrolides, prolonging the effects of the respiratory agents, macrolides, fluoroquinolones, beta-lactams for that matter. To prolong the useful lifetimes of these drugs, we need multiple drug choices for

respiratory infections. The more choices, the better.

Now, here we're talking about a new class of drug. I think the manufacturer is to be complimented for persistence in bringing forward a new class of drug. We certainly haven't had many of them, and that's very much what we need to stay ahead of the problem of drug resistance. We know manufacturers are dropping out of antibiotic production. If we set the approval barriers too high, we just won't have any more antibiotics in the pipeline. We can talk forever about appropriate drug use and all that, but if we don't have the new drugs in the pipeline, we're never going to get ahead of the problem.

Now, obviously efficacy and safety are the two most important considerations that have to be evaluated in an application for drug approval. But I think my feeling is that if there's some doubt, it would be helpful, particularly with a new class of drug, if it were possible to justify approval with some precautionary labeling. That would be very nice rather than disapproval.

DR. LEGGETT: Any comments around the table in general about the efficacy of this drug for the three indications? Anything different than the last time we went through this. Dr. O'Fallon.

DR. O'FALLON: One of the things that we haven't said that was sort of at the back of my head when I

was reading through the data was remember when we looked at this, sinusitis business, we've seen the Pollyanna effect and this one was not double-tapped and that type of thing, the equivalent thereof.

So I was sort of looking to see if the cure rates, these clinical cures, are more than what you would have expected from just using something as sloppy as clinical cure as an endpoint. It seemed to me the data really were higher than you would expect, the 70-ish percentage that we were talking about. These pretty much across the board seem to be higher. They were mostly 80 percent and up in the different subsets. And it seemed to me that spoke of a real effect. So throughout all this questioning, I thought that there really is pretty sound data of efficacy.

DR. LEGGETT: Yes, Dr. Elashoff.

DR. ELASHOFF: Well, I think the data establish that a lot of people were classified as having gotten better. I think they establish that the proportion who were so classified is no more than 10 to 15 percent less with this drug than with the comparators. But without data in front of us establishing the efficacy of the comparators, the data in front of us does not establish efficacy of this new drug.

DR. LEGGETT: Yes, Dr. Poretz.

DR. PORETZ: First of all, I'd like to thank Dr. Powers. That discussion was really helpful this morning. It really was.

From a practical point of view, I think telithromycin is at least as efficacious as any of the other drugs on the market, the comparators that they demonstrated for pneumonia, bronchitis, and sinusitis. And for that reason, I think it's going to be just as valid using that drug as anything else.

My hope would be that some of the drugs at the present time are obviously being overused. The macrolides are being tremendously overused in my area of practice in northern Virginia right over here. Everyone and their brother is being put on a macrolide or a quinolone, and I'm very, very concerned about it because even in my local hospital I've been watching the resistance rate go higher and higher and higher. I think that's really dangerous.

My only concern, a simple concern perhaps, is the visual problem because I think practically that could be a problem because as mentioned by the ophthalmology people a while ago, suppose someone wants to drive a car and they're trying to accommodate from looking forward and closer and so on. That could be a real problem and if someone got in an auto accident, crashed their car because of that, because of inattention because they couldn't

accommodate, that could be a social phenomenon, if you will, that could cause legal repercussions and a whole bunch of other things. And I think even though the incidence is less than 1 percent, 0.4 percent of whatever it is, I think it needs to be noted with significance, if you will, in the package insert or the PDR or whatever.

I'm not that concerned about QT prolongation. I think the discussion today showed it was no worse than anything else.

And the hepatotoxicity doesn't look like it's any worse than any other antimicrobial. My goodness, cephalosporins can raise liver enzymes in themselves.

So I'm particularly concerned about the visual aspect, and I think that needs to be somehow noted significantly in the package insert.

DR. LEGGETT: Given the way they drive in Italy, that might be the reason that none of it was reported.

(Laughter.)

DR. LEGGETT: It's okay. My wife is Italian.

Any further general statements before we pass on to the votes?

(No response.)

DR. LEGGETT: This is always the fun part. I think the voters are from here down to the end of the

table, not including Dr. Brown.

The first question is, do the safety and effectiveness data presented support the use of Ketek for the following indications? A, community-acquired pneumonia. And why don't we go around and everybody sort of puts in their 2 cents. Do you want to start, Jan?

DR. PATTERSON: I would say yes for those three indications. I think that the caveats that should be included in the label include the warning about rare instances of hepatotoxicity that's idiosyncratic and also the blurred vision which is more common in those less than 40 years old and more common in women. That should be specified in the label and perhaps some specific directions about not driving and doing other things that require clear vision the first 12 to 24 hours after the first dose.

And I think in consideration of the safety and efficacy, along the lines expressed by Dr. Bell, we need new agents and this one has a targeted respiratory spectrum that doesn't increase our concerns for Gram-negative resistance, and that enters into my decision.

DR. LEGGETT: I would echo that.

In addition, I would perhaps think about mentioning in the label something about limitation of the duration of the medication, to be on the safe side.

Then in terms of the visual effects, it was my

understanding from today that the data had come in so late that the FDA had not yet analyzed that. So I think there's probably still some more work to be done I think. At least in the packet that we got, there were several things that hadn't been analyzed yet, and today I thought that one of the statements was about the visual effects.

DR. SORETH: I think that one study or a set of studies that we haven't been able to analyze yet were those submitted December 31st which had to do with simvastatin and telithromycin pharmacokinetic information.

Secondly, with regard to post-marketing safety data, I think we need to get a more complete handle, since we have excerpts from Medwatch forms. I don't know that we have everything as yet in house because it's a dynamic thing. Reports come in on a regular basis, et cetera. At some point you have to lock the database, lock what time you say you're going to give things to the FDA, et cetera. So we need to get a better handle I think on the full scope of post-marketing reports, et cetera.

DR. LEGGETT: Thanks.

Oh, I forgot you, Bill.

DR. LEE: Yes. I would vote all three for yes, but I would certainly put on the package insert a comment about increased ALTs and possible hepatotoxicity. I think your point about the duration is important as well.

DR. LEGGETT: Do you want to do B and C while we're doing this on number 1?

DR. PATTERSON: I would say yes for those also.

DR. LEGGETT: That's three yeses.

Dr. O'Fallon.

DR. O'FALLON: I agree with what's been said so far.

For, Janet, Dr. Elashoff, this committee has seen data in the past that has tended to make us believe that these comparators are better than placebo, but I've seen some meta-analysis data at times that they've given us in other studies. But it wasn't presented here. Dr. Elashoff is absolutely correct. When you're comparing two different active drugs and saying are they different, that's great, but both of them could be terrible. Something has to show that at least one of them is generally active and better than a placebo, and we didn't have that data. She's correct about that, but we have seen something like that in other cases.

DR. LEGGETT: Barth.

DR. RELLER: I'd say yes for community-acquired pneumonia, no for acute exacerbations of chronic bronchitis, and yes for acute sinusitis.

My reservations about acute exacerbations of chronic bronchitis are twofold. One is it didn't make it

in my view for Haemophilus influenzae, which was the most common of the documented causes. The overall database is smaller than with any of the other indications. We voted 0 to 10 18 months ago, and I don't see a substantive improvement in the database for acute exacerbations of chronic bronchitis. And lastly, of all of these indications where the drug is apt to be used repeatedly it would be for this indication. That's my reasoning.

DR. LEGGETT: A clarification. One of the reasons we were 0 for 10 is we didn't have the safety data as well. Do you want to address that aspect? Is your no for the AECB based on the efficacy part and not the safety efficacy --

DR. RELLER: That's why I had my additional comments. My no is principally based on efficacy with that being driven largely by the results with Haemophilus influenzae, the overall relatively small numbers compared with the other indications, and a sprinkling of concern about safety given how often patients take drugs repeatedly for acute exacerbations of chronic bronchitis.

DR. LEGGETT: Thank you.

Dr. Maxwell.

DR. MAXWELL: Yes. I vote yes on community-acquired pneumonia. I vote yes on acute exacerbation of chronic bronchitis and acute sinusitis.

However, I have some concerns and believe that the labeling should be clear as to the adverse events that we mentioned and that there should be some more evaluation of the visual involvement in these patients and to look primarily at women to see if women present a different population, and there should be some kind of adjustment made based on that.

DR. LEGGETT: David.

DR. BELL: I vote yes for all three of them, pneumonia, chronic bronchitis, sinusitis, with the precautionary labeling dealing with the visual, cardiac, and hepatic manifestations that has been alluded to.

DR. LEGGETT: Alan?

DR. CROSS: I vote yes for community-acquired pneumonia. I share Dr. Reller's concern both about the data and other aspects that he mentioned in terms of chronic bronchitis. So I would vote no for that, but I would vote yes for the acute sinusitis. And I also agree that the labeling ought to highlight the visual aspects and the potential for hepatotoxicity, especially among those who already start with a baseline of a high ALT.

DR. LEGGETT: Dr. Wald.

DR. WALD: I vote yes for CAP and no for bronchitis and yes for sinusitis and agree with the recommendations about labeling specifically with regard to

the visual toxicity.

DR. LEGGETT: Dr. Rupp.

DR. RUPP: I vote yes for all three indications. I think the precautionary labeling should reflect what's already been discussed with regard to vision, prolonged dosing, perhaps some caveat on the frequency of repeated dosing, and the precautionary labeling with regard to hepatotoxicity and cardiac toxicity should be similar to the comparative agents.

DR. LEGGETT: Dr. Elashoff.

DR. ELASHOFF: I vote no on efficacy of all three since the data at hand do not establish the efficacy of the comparators. I would like to see if it is, in fact, approved the kinds of caveats that people have previously mentioned with regard to safety.

DR. LEGGETT: Don.

DR. PORETZ: I vote yes for community-acquired pneumonia. Although I have some reservations about chronic bronchitis, I think those are very, very difficult studies to do and compare, but it seems like it's just as efficacious as the other drugs that it was compared against. So I vote yes for that, and I vote yes for acute sinusitis with the same caveats that everyone else has said.

DR. LEGGETT: One thing that came to mind, when

you were talking about the low numbers, Barth, you were talking about the bacteriologic numbers or were you talking about the clinical cure rates? Because people alluded to that same problem all this time. We have the same clinical cure problem in all respiratory tract infections except for bacteremic pneumonia. Did you have specifically in mind the low clinical cure for Haemophilus or were you talking specifically about our low numbers of bacteriologic per-protocol numbers?

DR. RELLER: The data presented by the sponsor -- I mean, there were big differences between efficacy for Haemophilus influenzae, and it's a leading cause, not the only, but a leading cause among the big three for acute exacerbations of chronic bronchitis that one might expect to respond to antimicrobial therapy. I realize it's a complex clinical gemisch, but if there would be any benefit to antibiotics, it's for these organisms and a major one is found wanting.

DR. LEGGETT: Let me pursue this a second. I'm trying to fish it out for them. Should the H. flu in pneumonia be different from the H. flu in chronic bronchitis? Is there something that you're alluding to, or is it that we just can't look at it as much?

DR. RELLER: Well, I mean, on theoretical grounds, why would it possibly work in one? I mean, I'm

only going by the data that we have before us. I'm not speculating. I think the charge is based on the data presented, what do you think, and I told you what I thought.

DR. LEGGETT: I'm not trying to put you on the spot. I'm just trying to flesh it out.

Number 2, and Don, we'll start with you. Do the safety and effectiveness data presented support the use of Ketek for the treatment of penicillin-resistant Streptococcus pneumoniae for the following indications: community-acquired pneumonia and acute sinusitis? If yes, are there any special caveats on the label? If no, what other information would be required?

DR. PORETZ: I vote yes in favor of both. I do think we need drugs in our armamentarium, especially on an outpatient basis, to put patients on. Again, I'm very concerned about overusage of quinolones, and I'm concerned about the other macrolides being used. I think this is another drug that can be used safely to keep someone out of the hospital to treat them with an oral medication. So I vote yes for both.

DR. LEGGETT: And the label would be the same?

DR. PORETZ: Yes.

DR. LEGGETT: Dr. Elashoff.

DR. ELASHOFF: No.

DR. LEGGETT: Presumably for the same reasons?
DR. ELASHOFF: Yes.
DR. LEGGETT: Dr. Rupp.
DR. RUPP: I vote yes for both those indications for penicillin-resistant Strep. pneumo.
In addition, I guess I would add a caveat that I didn't mention before, that for community-acquired pneumonia, it should be for mild to moderate disease.
DR. LEGGETT: Dr. Wald.
DR. WALD: I feel a little bit worried about the overall reported activity against resistant cases. We have an overall cure rate of 70 percent for all comers with resistant pneumococci and that's not different from the preliminary data a couple of years ago. And for the bacteremic, well, we just have so few. So I would not recommend it for resistant cases.
DR. LEGGETT: And that goes for both of them. Ellen, that's for both? Yes.
DR. WALD: Yes.
DR. LEGGETT: Dr. Cross.
DR. CROSS: I would vote yes for both.
DR. LEGGETT: Dr. Bell.
DR. BELL: I would vote yes for both and would agree that it's for mild to moderate pneumonia.
DR. LEGGETT: Dr. Maxwell.

DR. MAXWELL: I would also vote yes for both and agree to the indication for mild to moderate.

I would have liked to have seen, though, if it were possible, because I believe this is the kind of drug that would be used in patients that are HIV positive, some comparison on patients that are taking either protease inhibitors or something like that to see if there is a difference.

DR. LEGGETT: Barth.

DR. RELLER: I vote no, and the reason is not because I don't think that it works. I feel actually more strongly about this than I did about the other issues, and that is because I believe that separating these out specifically is not necessary.

DR. LEGGETT: Separating what?

DR. RELLER: This has to do with the labeling.

DR. LEGGETT: Okay.

DR. RELLER: That is, denoting that these are efficacious is not necessary nor in my view are the data sufficient to do that. My reasoning is this, that the way I would label this compound, which I do believe works for community-acquired pneumonia, is that it would be approved for susceptible pneumococci, and if 98 percent of pneumococci are susceptible, even though some of those that are susceptible may be resistant to penicillin or resistant

to erythromycin by this mechanism or that, so be it. But to designate it separately gives the impression to me that there's something special about this drug that makes it really super, and I don't think we have the comparative data. That is, special for those resistant strains. I don't think we have the comparative data for that, that is, the direct comparison.

And moreover, based on the compounds that have got that designation before, though it's not a direct comparison, the success rates are far better for every indication than what the data are here.

So I think to single out this as being the implication that it has special utility against resistant organisms, as opposed to saying it works for telithromycin-susceptible organisms, would be the wrong thing to do.

DR. LEGGETT: Dr. O'Fallon.

DR. O'FALLON: I agree with what Dr. Reller has said, but my reasons are a little bit different.

First of all, you know that I wasn't very happy when we approved those other ones. The sample sizes were pitiful, and these are better. They really are better. So, again, great. That's a lot of improvement but it isn't very good. These numbers are not very big.

And the thing that really bothered me was that presentation this morning in which there was a question as

to whether the sensitive and resistant and so on organisms result in different outcomes of disease. Given that, the underlying real uncertainty about the usefulness of this designation to begin with, I don't think we should go there yet. If it proves to be important, then we can come back and deal with it, but right now I don't think there's enough information and there is a real question as to how important that difference is in the real world.

So I vote no. I agree with what Dr. Reller said.

DR. LEGGETT: My vote is no for the following reasons. This drug is going to be used empirically before we know whether the bugs are resistant or not, so it makes no sense clinically. The pneumococci are multiply resistant more than they are, so does the next company come back and say, well, we warrant something for TMP sulfur-resistant pneumococci? It doesn't make a lot of sense.

And we have seen emergence of resistance over time. We've seen MIC creep for amoxicillin and penicillin. We are in the process of seeing MIC creep, or at least efflux creep, for the macrolides, and we're now seeing the emergence of resistance of fluoroquinolones.

So I think for me the proper way to approach this would either be to just say for penicillin-susceptible pneumococci. But to me the better way would just be to say

Streptococcus pneumoniae and not specify the susceptibility.

Dr. Patterson.

DR. PATTERSON: I would vote yes for mild to moderate community-acquired pneumonia and yes for sinusitis. Entering into my decision would be that although the therapy is indeed empiric most of the time, our decision making in empiric therapy is based on people's risk factors for drug-resistant Streptococcus pneumoniae which are becoming more and more clear.

Also, in terms of a special caveat that should be included on the label, I think it would be worth saying that it may not be active against strains that are both penicillin-resistant and macrolide-resistant, and that's based on the data on pages 25 and 26 of the FDA briefing package.

DR. LEGGETT: You did such a good job with that one. Do you want to jump right to 3?

Oh, I forgot him again. There's a blank space there, and so I stop. Sorry.

DR. LEE: I would vote yes for both indications. I think we're going to see more resistance in future years, and I think the in vitro data is supportive that this works, although I take the point of the ID specialists who know more about this than I do, that the

real problem is simply facing up to Strep. pneumoniae.

DR. LEGGETT: Do you want to start off number 3, Bill? This is the macrolide part.

DR. LEE: I would say yes for both of those as well.

DR. LEGGETT: Jan.

DR. PATTERSON: I would say yes for both. I would also add, based on the discussion that we had earlier about the influence of resistance on virulence and outcome, I'm not convinced that resistant organisms are any less virulent than susceptible ones, and so they're still quite significant.

And the special caveat would be parallel to what I just said for PRSP in that strains that are macrolide-resistant and penicillin-resistant -- it may be less effective against those strains, again based on that same data.

DR. LEGGETT: To catch up for both of you, what would you say about a public health impact of having an additional new class of drug in terms of macrolide resistance, sort of what David was referring to earlier?

DR. LEE: I would just support what David said. I don't have any other additional comment.

DR. LEGGETT: And you, Jan?

DR. PATTERSON: I think that antibiotic

heterogeneity and the use of different classes of agents is probably an important factor in trying to decrease the emergence of resistance.

DR. LEGGETT: My comments for number 3 really are about the same as they are for number 2.

A little worry that I had, until we can sort out this NCCLS sort of thing, was the sort of higher MIC creep on the erythromycin-resistant pneumococci as opposed to the erythromycin-susceptible that was shown in the slide this morning. I'm worried about what the implications of that are, but for how this drug is going to be used, I don't think we need the label of erythromycin-resistant use.

Dr. O'Fallon.

DR. O'FALLON: My concerns about the previous are the same for this, and so yes, I vote no.

DR. LEGGETT: Dr. Reller.

DR. RELLER: No. I would prefer that local antibiograms that guide empirical therapy, consensus statements, guidelines similarly, and marketing prowess would point out where this drug might work for patients whose organism, if it were recovered, may be resistant to existing macrolides. But to point this out specifically I would not do.

Moreover, I am like Dr. Leggett wary of the

creep associated with the macrolides, and I'm skeptical of how robust a statement like this may be with widespread use.

DR. LEGGETT: Dr. Maxwell.

DR. MAXWELL: I vote yes for both of them. However, I would encourage the labeling to be such that widespread use or indiscriminate use is, as best as possible, avoided and the other concerns that I had for the toxicities be addressed.

DR. LEGGETT: Dr. Bell.

DR. BELL: I vote yes for both of them somewhat reluctantly because, A, I wish we had more cases, but of course, that's what we have. And we do have the in vitro data and some pharmacokinetic data. So I think that's okay.

I'm somewhat uncomfortable with this creep, you know, a formal indication for yet another drug that it becomes resistant to. On the other hand, that bridge was crossed with levofloxacin, and I don't know exactly how to go back now. So I vote yes.

DR. LEGGETT: Just an aside. We've burned bridges in past wars too.

(Laughter.)

DR. LEGGETT: Dr. Cross.

DR. CROSS: I vote yes for both. I too would

like to see more data but we're not going to have that. It's nice to have data on individual patients, but I agree with Jan and you, Jim, that this will be used empirically. And I think it's helpful data to know that if in your community or in your hospital there are macrolide-resistant Strep. pneumoniae, that this will be useful for that. So for that reason I would say yes for both.

DR. LEGGETT: Before we go on, Alan, in the label I guess the question is, is there a possibility to say that this drug has shown efficacy in limited numbers of patients with penicillin and erythromycin resistance? Is that something that can be put in without putting a label of "approved for"?

DR. SORETH: Well, I think basically if you have statements in the label that there is experience with it, it's basically something that can be advertised. We've tended in recent years to shy away from limited experience, less than 10 isolates, et cetera. So it's either in or out basically.

DR. LEGGETT: Yes. Well, you guys are writing the label, not us.

DR. SORETH: That's why they pay us the big bucks.

(Laughter.)

DR. LEGGETT: Dr. Wald.

DR. WALD: Will the label contain the information that for all PRSP, there was a 70.4 percent cure?

DR. SORETH: Labels can contain clinical study sections in which a fair amount of detail is given.

DR. WALD: I would advise that the label include that statement, and I would again vote no for both.

DR. LEGGETT: Dr. Rupp.

DR. RUPP: I vote yes for both. I think that antibiotic-resistant pathogens are clearly clinically significant. They're going to increase. We need additional choices, and I agree with many of the comments that my colleagues have made here with regard to the labeling. To me it's to a large degree a matter of semantics. Either you say it's indicated for susceptible organisms -- I think that would be the best way of doing it, but the precedent has been set. So other products are labeled as indicated for penicillin-resistant pneumococcus, and so I think we follow suit. And I would say yes for both of these.

DR. LEGGETT: Dr. Elashoff.

DR. ELASHOFF: No for both for previously stated reasons.

DR. LEGGETT: Last but not least.

DR. PORETZ: I vote yes for both because again

I keep seeing more resistance in my area, more quinolone use. I'm still scared of quinolone use empirically for everything, and I think this gives practicing doctors and nurse practitioners, whomever an added sense of security that perhaps they are at least playing the odds that the organism is going to be sensitive.

DR. LEGGETT: So you're using Dr. Bell's public health thing, the more options you have, so you don't just have to use fluoroquinolones?

DR. PORETZ: I think the practicing prescribing physician needs some added protection, at least odds-wise, as far as active against the Strep. pneumoniae.

DR. LEGGETT: Since we, as usual, were unanimously probably split down the middle, I think that is another option that the FDA could consider in whether they label it or not, the implications of having another class of drugs besides fluoroquinolones that would have a label such as that. And you can weigh the pros and cons of something like that.

DR. LEE: Are you ready to start on the next thing? Because I have to leave.

DR. LEGGETT: Go to number 4? Sure.

DR. LEE: My only suggestion for additional studies would be kind of following on from my comments and Dr. Reller's comments that it might be well to track these

multi-use cases and particularly maybe focus on the AECB cases for tracking evolution of liver toxicity and possibly also looking at if there's a reason to treat HIV patients to use this drug -- I'm not sure there is right now, but if there were instances of use in HIV, that would be the other at-risk population I think.

DR. LEGGETT: Jan.

DR. PATTERSON: As Celia mentioned, I think studies of the visual effects, the mechanism of that and, in particular, why this previously unseen effect of accommodation or lack of is more common in women, and to track those who get repeated dosing of this agent, and also, as Celia mentioned as well, to look at it with protease inhibitors, particularly those that we know are liver toxic.

DR. LEGGETT: My comment about HIV is that I'm not going to be using it anytime soon on my patients with protease inhibitors until I let everybody else figure out if it's toxic.

Dr. O'Fallon.

DR. O'FALLON: No.

DR. LEGGETT: Nothing for Dr. O'Fallon.

Dr. Reller.

DR. RELLER: Among the toxicities, the one that I'm most cautious about is the visual disturbances. One of

the things that I think through some mechanism needs to be sorted out as to whether, if it's going to occur, it occurs after the first dose or whether there is any cumulative or it's unpredictable because if one is going to have any caveats in the label, it would be helpful to be able to spell them out more precisely. That is, this unusual event or rare event or whatever the frequency is may be seen after the first dose and it lasts this long so that you can put some reasonable boundaries. I mean, if one is taking the drug for 5 days or 5 to 10 days, does that mean that one needs to be cautious about it, and does it come on without any warning? Does it start out that you have a little bit of trouble accommodating and then more trouble accommodating?

And I don't want to blow this out of proportion in terms of how frequent it is, but the implications with drugs that are used in the millions, not necessarily would this one be, though that's every sponsor's dream in terms of market share, but in the aggregate there are tens of millions of prescriptions for the indications that are given.

I think if it's transient, if it happens, it either happens or it doesn't happen right away, and it lasts no more than 12 hours, then it puts some common sense into the labeling as opposed to it could happen anytime

during the course and it may last days. You get the idea.

DR. LEGGETT: Dr. Maxwell.

DR. MAXWELL: I underscore the comments of my colleagues. I would like to add particular emphasis, though, on the fact that I think this seems to preferentially impact on women somewhat differently and no one has been able to give me a clear explanation as to why. So I think that studies that look at women more closely going forward would be something that would be important.

DR. LEGGETT: Dr. Bell.

DR. BELL: Yes. I think particularly since this is going to be mostly used as an outpatient, the studies that Dr. Reller and Maxwell have alluded to are particularly important, risk factors for the toxicity. It's young women. Can anything else be said besides that about who is at risk and then a better description, as Barth has pointed out, of the timing and so on.

DR. LEGGETT: Dr. Cross.

DR. CROSS: I would agree with the need for more visual studies on the lines that have already been mentioned by my colleagues.

DR. LEGGETT: Ellen.

DR. WALD: I agree.

DR. LEGGETT: Mark.

DR. RUPP: I would encourage the sponsor to

continue a robust surveillance network. I'm concerned that already we're talking about 1 percent pneumococci being resistant to this compound. I think it's very important to track that. I would also say if there's any way -- I don't know if it's logistically possible, but to track patients who have had repeated courses of telithromycin to see if it amplifies any of the possible toxicities would be suggested.

DR. LEGGETT: Or amplifies resistance.

DR. RUPP: That as well.

DR. LEGGETT: Dr. Elashoff.

DR. ELASHOFF: I would support the previous committee members' suggestions about additional studies.

DR. LEGGETT: Don.

DR. PORETZ: The only thing I would add would be ongoing surveillance for drug interactions. In the package insert in Europe in our briefing book, they talked about actually stopping statins while people are taking the drug. A lot of people on statins in the United States, a lot of people on lots of drugs, a lot of transplants in this country. I think drug interactions is a major, major problem that needs to be watched.

DR. LEGGETT: Yes, I would assume that the label is going to talk about cyclosporine A and those sort of things.

Do you want to give us a tally?

DR. TURNER: The tallies for the questions are as follows.

For question number 1, we had 8 votes of yes for all three indications; 3 votes of yes for all except chronic bronchitis; and 1 vote of no for all three indications.

For question number 2, we had 7 yes votes for both indications and 5 no votes for both indications.

For question number 3, we had 7 yes votes for both indications and 5 no votes.

DR. LEGGETT: Dr. Soreth, what would you have us do at this point?

(Laughter.)

DR. SORETH: Go back to your hotel room and relax.

(Laughter.)

DR. LEGGETT: Thank you.

(Whereupon, at 4:35 p.m., the committee was recessed, to reconvene at 9:00 a.m., Thursday, January 9, 2003.)