[Slide.]

This table of clinical cure rate by risk subgroup demonstrates the effectiveness of telithromycin in those subjects at increased risk of morbidity and mortality.

[Slide.]

Finally, in acute bacterial sinusitis, pre-approval clinical efficacy data, including a total of 458 subjects in 3 randomized controlled pivotal Phase III studies demonstrated that telithromycin is effective in treating infections due to key common bacterial pathogens and in outpatients at risk of complications, for example, those with investigator-assessed severe infection, pathogen identified at entry, or opacity on sinus X-ray.

The next two slides will demonstrate some of the key data that we used to support the efficacy of telithromycin in the treatment of acute bacterial sinusitis.

[Slide.]

As you can see in this table, the clinical

cure rates for telithromycin were comparable to those for amoxicillin/clavulanate or cefuroxime. Overall, the clinical cure rates for telithromycin and comparator were higher in Studies 3011 and 3002. These studies included bacteriologic cultures by sinus puncture aspirate or endoscopy.

[Slide.]

Data in this table demonstrate the effectiveness of telithromycin in those subjects who are at increased risk of complication from acute bacterial sinusitis.

[Slide.]

Overall, in the 14 Phase III efficacy studies, telithromycin was shown to be effective for the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis and acute bacterial sinusitis, as well as for the treatment of community-acquired pneumonia due to multidrug-resistant Streptococcus pneumoniae and in outpatients with these respiratory tract infections who are at risk for complications.

Next, I will discuss the clinical safety

data that were used to support the FDA approval of telithromycin.

[Slide.]

To establish the safety of telithromycin prior to approval, we conducted a comprehensive clinical development program, collected and evaluated data from postmarketing surveillance following the approval of telithromycin in the EU in 2001 and developed and implemented a risk management plan that will be further discussed by Dr. Barbara Rullo.

[Slide.]

Safety data to support the FDA approval of telithromycin included clinical trial data for more than 4,700 telithromycin-treated subjects in pivotal Phase III studies including more than 2,700 in randomized controlled trials, as well as ex-U.S. postmarketing safety data following an estimated 6 million patient exposures.

Additional information that we submitted to the FDA included clinical trial data from telithromycin-treated subjects in other studies,

for example, in the pediatric program or in Japan, German postmarketing survey data, as well as Study 3014, which due to data integrity issues was not used for approval but, nevertheless, provided some additional information regarding characterization of specific adverse events of special interest.

[Slide.]

In the Phase III studies, the most frequent adverse events in both the telithromycin and comparator-treated groups were gastrointestinal, for example, diarrhea, nausea, and vomiting.

[Slide.]

The frequency of adverse events leading to discontinuation and more serious adverse event including those leading to death were similar in the telithromycin and comparator treated groups. There were no investigator-assessed treatment-related deaths in either treatment group.

[Slide.]

During clinical development, we identified several safety topics as adverse events of special

interest: hepatic and cardiac--that is to say, QTc-related adverse events based on review of preclinical, clinical pharmacology and/or clinical data, as well as the known effects of the related macrolide class;

Visual adverse events based on Phase III randomized controlled studies and exacerbation of myasthenia gravis via postmarketing surveillance.

[Slide.]

With respect to the hepatic adverse events we noted a preclinical effect consistent with what is observed with macrolides, like erythromycin from which telithromycin is derived. This was closely followed up in clinical trials.

One report of hepatitis with a biopsy that showed granulomatous hepatitis with eosinophil granulocytes was discussed in detail at both meetings of the advisory committee. Follow-up information that we obtained on this initial case of concern provided details that indicated a likely pre-existing autoimmune hepatic disorder that was unrelated to telithromycin therapy.

After an estimated 6 million postmarketing patient exposures, there had been no reports of drug-related hepatic failure, death, or liver injury resulting in transplantation.

[Slide.]

Pre-approval data showed that the hepatic safety of telithromycin is comparable to other antibiotics prescribed for similar treatment indications and was appropriately characterized in the initial labeling.

[Slide.]

Turning now to cardiac or QTc related adverse events, preclinical studies, as well as extensive clinical pharmacodynamic studies that evaluated the cardiac effects of telithromycin, showed that prolongation of the QTc interval, an electrocardiographic abnormality that was comparable to macrolide antibiotics even in at-risk populations with a 1.5 millisecond increase calculated using Bazett's formula at a therapeutic dose.

The isolated reports of torsades de

pointes and ventricular fibrillation with a combined reporting rate of approximately 1 case per million either lacked information to establish a diagnosis or were confounded by coadministration of other medications known to affect cardiac repolarization, significant underlying cardiac disease, or concurrent illness which might otherwise explain the event.

[Slide.]

As mentioned previously, visual adverse events were first identified in clinical trials. Subsequent Phase I studies revealed a mechanism of action that was consistent with a transient delay in accommodation and after an estimated 6 million exposures prior to approval, there had been very rare postmarketing reports of severe visual adverse events with no objective eye injury or persistent ocular sequelae.

[Slide.]

In clinical studies, there was no patient with myasthenia gravis. The safety signal for myasthenia gravis was detected with the assistance

of the French pharmacovigilance system approximately 5 months following the launch of telithromycin in France.

Based on these rare reports of exacerbation of myasthenia gravis including reports of respiratory failure, we updated the EU labeling, issued a Dear Health Care Professional letter and communicated the risk to myasthenia gravis organizations.

The warning in the initial U.S. prescribing information was consistent with what had already been adopted in the European Union.

[Slide.]

To summarize, the large clinical experience prior to FDA approval revealed an overall safety profile for telithromycin that is similar to marketed antibiotics with gastrointestinal events being the most common adverse events and a low discontinuation rate.

Adverse events of special interest, hepatic, cardiac and visual adverse events, as well as exacerbation of myasthenia gravis, were well

characterized in the initial U.S. labeling, which included a patient package insert.

[Slide.]

Adverse events described in the Warnings and Precautions Sections of other antibiotics, as was mentioned by Dr. Jenkins, were not in the label for telithromycin, such as tendon rupture, fluoroquinolone, or anaphylaxis for the beta-lactams.

[Slide.]

Postapproval regulatory activities have included following up on our postmarketing commitments to the FDA.

[Slide.]

We submitted an 18-month visual safety update report in October 2003, which characterized the worldwide postmarketing spontaneous reports of adverse events. These findings were consistent with the pre-approval findings and will be discussed in more detail by Dr. Rullo.

[Slide.]

In accordance with the Pediatric Research

Equity Act, we conducted clinical trials to gain experience in the pediatric population.

The pediatric Phase III studies, as was mentioned by Dr. Cox, were voluntarily paused in June 2006 pending final confirmation that the pediatric development program is consistent with the current thinking of the FDA regarding evolving guidances for appropriate clinical trial design and planning for antimicrobial drug development and approval.

There was no safety signal identified by Sanofi-Aventis or the independent Data Monitoring Committee, which is chaired by Dr. George McCracken, who will be here tomorrow.

There was no reason to warrant suspension of these pediatric studies.

[Slide.]

The Telithromycin Risk Management Plan, this is important to mention. This was conceived prior to approval and submitted at the time of FDA approval.

It has been developed and has been

continuously updated and implemented to detect unexpected and rare adverse events, to regularly update telithromycin's safety profile, to facilitate access to information.

We continually monitor adverse events of special interest to further characterize them in clinical practice environments and to compare their occurrence to other antibiotics prescribed for similar indications.

In addition, as you will hear later from Dr. Jenkins, the risk management plan provides for ongoing microbiologic surveillance of antibiotic-resistant patterns in the U.S. and worldwide.

[Slide.]

Finally, in conclusion, with respect to the FDA approval activities, we have completed a comprehensive clinical development program and fulfilled our postmarketing commitment to evaluate reports of visual adverse events for 18 months following the launch of telithromycin in the U.S.

We continue to rigorously monitor and to

diligently assess the safety profile of telithromycin using multiple data sources and methods including spontaneous reports, the FDA Freedom of Information database and other epidemiologic databases.

You will hear more about this later from Dr. Rullo and our external experts Dr. James Lewis, Randy Kardon and Donald Saunders.

We also continue to perform prospective microbiologic surveillance studies to assess patterns of antibiotic resistance, which you will hear more about from Dr. Stephen Jenkins.

Thank you.

DR. EDWARDS: Thank you, Dr. Edelberg.

We are going to turn now to the FDA presentations, which will be initiated by Dr. Janice Soreth, who is the Director of the Division of Anti-Infective and Ophthalmology Products.

FDA Presentation

DAIOP Presentation on Ketek Data & Review

Regulatory History

Janice Soreth, M.D.

DR. SORETH: Thanks, Dr. Edwards.

[Slide.]

What I would like to do today is to give an overview from the FDA perspective of the regulatory history of telithromycin or Ketek, about which you have already heard quite a bit.

The U.S. submission started in 1998 with the IND filing through to 2004, with the U.S. approval, and that entailed 3 review cycles. I will talk about those in addition to the two Advisory Committees that we held in April of 2001 and January of 2003, talk a little bit about the Division of Scientific Investigation Reports and I will leave the specifics of the efficacy and safety data through pre-approval, as well as afterwards, to a presentation by Dr. John Alexander.

Dr. John Alexander's presentation, as well as others throughout the next two days, I think will help us to try to answer a simple question that I think doesn't have a simple answer, the "compared to what" question: How does Ketek stack up in efficacy, how does Ketek stack up in terms of

safety compared to other marketed antibiotics?

[Slide.]

The first cycle began with the IND filing to us in U.S. in 1998. Later that year, the company met with us to discuss clinical trials for their Phase III development program. You have already heard that that entailed 4 indications: community-acquired pneumonia, acute bacterial sinusitis, acute exacerbation of chronic bronchitis and tonsillopharyngitis.

Our advice to the sponsor at that time on specific trial design was based on the then current 1998 updated guidance. Let me digress for a moment down memory lane just to mention what that was about.

It was affectionately called the 18 wheeler, because it was a 2-year FDA effort to update anti-infective guidances. At that time, FDA reviewers rolled up their sleeves, worked with Special Government Employees and then committee members of the Anti-Infective panel, divided up the guidances and I think, with a great amount of

determination and grace, published drafts in the Federal Register, got comments from the public, academia and industry, and spent three days in a public advisory committee meeting then in 1998, chair by Dr. William Craig, to try to improve trial design in the study of patients with various infections.

This necessarily included discussions of community-acquired pneumonia, acute bronchitis, acute exacerbation of chronic bronchitis and acute sinusitis, the same controversial topics we have heard talked about today were talked about then.

What were some of these? What exactly is the size of the treatment effect in indications like acute bacterial sinusitis or acute exacerbation of chronic bronchitis, or acute bronchitis, an indication we no longer grant?

Can we ensure the safety of patients if we go down the route of placebo-controlled trials, particularly if we include more severely infected patients? How do we balance the potential side effects of antibiotics with the potential

complications of no treatment, again, particularly if we include sicker patients?

How do we convince U.S. IRBs to sign on lest we drive trials like this, including placebo-controlled trials, offshore, raising the appropriate ethical concerns of experimentation outside of the U.S.?

None of these issues have easy answers. But they arose in discussions in the '90s, just as they are topics of discussion and controversy today.

With that as the backdrop, then, based on the available data to the Committee and to us, including limited literature studies of placebo-controlled trials, the Committee's advice to us in the latter '90s was as follows.

For acute bronchitis--back then it had a longer name, secondary bacterial infections of acute bronchitis--for acute bronchitis, the literature were clear, it's a viral entity and it needed to be studied exclusively in placebo-controlled trials if it was to be an

indication granted at all. We chose not to continue to grant it.

At that point, the Committee advised us for community-acquired pneumonia, acute exacerbation of chronic bronchitis and acute bacterial sinusitis, their view of the meta-analyses at that point in time in the latter '90s, supported continuing to do active controlled trials particularly when sicker or more severely infected patients were to be included, the very population they and we thought most likely to derive benefit from antibiotics.

With that as the backdrop, then, we advised Aventis and other companies at that time to continue on the path of active controlled trials trying to be as strict as we could with case definitions, proving at baseline that patients had bacteria and including in those updated guidances measures to evaluate patients as best we could.

[Slide.]

In 2000, then, the FDA received from Aventis their NDA application and in 2001, an

Advisory Committee was held.

What did we did we discuss then? The four indications about which you have heard.

[Slide.]

It included a discussion of 13 Phase III clinical trials across the then requested 4 indications with at least 2 controlled trials in each of the indications, with a safety database of roughly 5,000 patients.

[Slide.]

There were a little over 3,200 patients who had been exposed to Ketek and 1,600 exposed to different comparators. That broke down into about 2,000 patients on Ketek in controlled clinical trials and another 1,200 patients in uncontrolled trials on Ketek.

[Slide.]

The focus at the April 2001 Advisory Committee meeting was largely on safety. The FDA presented its efficacy analyses consistent with those of the sponsor for community-acquired pneumonia, acute exacerbation of chronic bronchitis

and acute bacterial sinusitis.

A study in tonsillopharyngitis did not meet its prespecified endpoint and we tabled further discussion of that indication.

The Advisory Committee in 2001 did not take issue with efficacy data derived from non-inferiority trials for that was the standard at the time.

[Slide.]

What were the chief safety concerns? Both from preclinical data, as well as the clinical trials, there were signals for cardiac toxicity including QT prolongation, as well as hepatic toxicity. In the clinical trials, the signal for visual adverse events, blurring, et cetera, was noted.

[Slide.]

When we put before the panel the question, do the efficacy and safety data presented support the use of Ketek in community-acquired pneumonia, the majority voted Yes, however, the majority voted No for acute bacterial sinusitis and there were no

votes for approval at that point for acute exacerbations of chronic bronchitis.

The Committee clearly wanted more safety data and specifically, in a couple of areas, more efficacy data.

On the question of whether or not there was sufficient evidence to approve the drug for penicillin-resistant Strep pneumoniae, the majority voted No.

[Slide.]

The recommendations of the 2001 Anti-Infective Advisory Committee to us were as follows.

Look at a larger number of patients and study them to really understand the safety profile of the drug. Include and target special populations, the elderly, patients with hepatic and renal impairment, and do more to elucidate the pharmacokinetics, study drug-drug interactions.

On the efficacy side, the Committee requested that we ask for more experience in patients with drug-resistant Strep pneumoniae, more

patients with Haemophilus influenzae particularly in acute exacerbation of chronic bronchitis.

[Slide.]

In 2001, in June, we issued an Approvable letter for CAP, AECB and sinusitis. We asked for additional safety and efficacy data, as had been recommended to us by the Committee, a larger trial capturing patients with various respiratory tract infections, PK studies including special populations, and greater experience with Strep pneumoniae with patients with concurrent bacteremia and Haemophilus influenzae.

[Slide.]

The second cycle of review, then, was prompted by a resubmission that included Study 3014, 24,000 patients, over 1,800 investigators, data from additional efficacy studies in community-acquired pneumonia, AECB, PK studies, and some postmarketing data.

On January the 8th, 2003, we discussed data at a second Advisory Committee meeting.

[Slide.]

That data included additional efficacy and safety as outlined in Study 3014, in addition to PK studies, and in studies of community-acquired pneumonia targeting resistant Strep pneumoniae and bacteremia.

[Slide.]

The Advisory Committee then, in January of 2003, judged that safety and efficacy for the three requested indications had been demonstrated and that was, in large measure. on the safety data in Study 3014.

What we were not at liberty to discuss at that point in an open public hearing was what we got in a report from the Division of Scientific Investigation two weeks later, January the 21st, 2003, a report of 3 routine investigations of 3 clinical sites where red flags were raised about data integrity.

Had we had discussions with our colleagues before this with DSI as the investigations were unfolding? Yes, for divisions are working together and we talk, and we e-mail, and we pick up the

phone. But the timing of the report of what was beginning to come into greater focus was two weeks after the Advisory Committee.

[Slide.]

Knowing that at that point, we needed to have a full appreciation of what went on in Study 3014, we could not fully assess the safety of the package and we issued an Approvable letter.

In that Approvable letter to the company, we raised questions of data integrity and we also asked for more complete postmarketing safety data to be submitted from foreign marketing experience.

We specifically requested of the sponsor for additional information on the auditing, monitoring and any irregularities or violations of Good Clinical Practices in order to further evaluate the data integrity of Study 3014, and we asked for complete reports, both original and follow-up, with regard to foreign postmarketing data that was clicking by outside the United States.

[Slide.]

A month later we held a CDER regulatory briefing within the FDA. A CDER reg briefing is a meeting that a division or office can call. It's an internal meeting of the FDA in which we ask the advice of senior management across the spectrum of office directors of the Center for Drug Evaluation.

The advice that we received from the CDER regulatory briefing I have quoted here from the minutes of the meeting.

"The issues of data integrity with Study 3014 are of concern and should be resolved before an approval action (if warranted) can be taken.

"Additional sites should be identified for future DSI inspections.

"If data provided by Study 3014 cannot be used to support the safety of Ketek, the Division might be able to rely on postmarketing data from those countries where Ketek has already been approved."

[Slide.]

A month later, in a closed session of the Anti-Infective Advisory Committee meeting, held to

talk about other development programs within the division, we apprised the Committee at that point in time of the data integrity issues regarding Study 3014 that precluded our approval action.

We brought it up then because we understood that your advice to us in January of 2003 had been to approve the product and whenever we take an action that is not in keeping with the very advice that you have worked hard to give us, I think we owe you some explanation of why we take a particular action that we do.

[Slide.]

The third cycle of review began then or continued when, in October of 2003, the sponsor submitted analyses of foreign postmarketing data.

Additional inspections of DSI were requested in order to provide us with an overall assessment of data integrity in Study 3014.

The report of DSI investigative efforts came to us in March of 2004 and it concluded that monitoring of study sites by the sponsor failed to detect problems found by FDA inspections when they

clearly existed. Hence, the integrity of data from all of the 1,800 investigative sites in that study could not be assured with any degree of confidence and we did not rely on those data to take a regulatory action.

[Slide.]

Instead, the focus of the review at that point became the safety information from the postmarketing experience that was clicking by in countries outside of the U.S. This included an estimated 3.7 million uses in foreign countries of which 2.2 million were in France and Germany, companies where our understanding of pharmacovigilance is that it is vigilant.

All the available safety data that we reviewed then led us to the conclusion that Ketek appeared similar to other antibiotics in terms of hepatic and cardiac toxicity in April of 2004. It was from the foreign postmarketing experience that we became aware of life-threatening exacerbations of myasthenia gravis with the use of Ketek.

The review of all available safety data

then supported approval of Ketek in April of 2004.

[Slide.]

In summary, then, these were the data upon which we have relied to provide us with substantial evidence of efficacy and safety for Ketek at the time of approval.

There were multiple comparative studies of community-acquired pneumonia, acute bacterial sinusitis and acute exacerbation of chronic bronchitis.

These comparative studies were the basis for the efficacy claims in those indications and they also served as the basis for safety claims, providing information on the rates of adverse effects seen with Ketek compared to other antibiotics used for these indications.

[Slide.]

Non-comparative studies of community-acquired pneumonia with Ketek were also taken into account. These were studies that targeted patients with multidrug-resistant Strep pneumoniae, and we used that safety data, as well.

[Slide.]

There was a Phase I visual study of higher doses of telithromycin to ramp up exposure performed to try to elucidate the mechanism of the visual adverse effects of the drug. There were multiple other Phase I studies evaluating the pharmacokinetics of Ketek that included food effect studies, drug-drug interactions, QT prolongation and studies of the pharmacokinetics of Ketek in patients with renal or hepatic impairment, a so-called "stack the deck" study.

[Slide.]

Finally, we relied upon foreign postmarketing data in 3.7 million exposures evaluated as part of the assessment of safety to identify uncommon serious adverse effects namely, hepatic, visual and cardiac, based upon postmarketing reports from France, Germany, other European countries and Latin America where Ketek was already approved.

[Slide.]

Now, I would like to turn the podium over

to John Alexander for the specifics of that efficacy and safety data.

Thank you.

Pre-Approval Efficacy and Safety Data

John Alexander, M.D.

DR. ALEXANDER: Good morning. My name is John Alexander. I am a Medical Team Leader in the Division of Anti-Infective and Ophthalmology Products.

It is my job to go over about four years of pre-approval safety and efficacy reviewed by the FDA in about 30 minutes, so this is going to be a quick run through.

[Slide.]

In terms of handling my topic, I am going to start out with discussing the efficacy data for each of the approved indications: acute exacerbation of chronic bronchitis, acute bacterial sinusitis and community-acquired pneumonia.

I will also touch on the information that we had available for us with regard to multidrug-resistant Streptococcus pneumoniae within

community-acquired pneumonia.

Then, I will move on to the safety data focusing mainly on the controlled clinical trials, safety information that we had and information from the foreign postmarketing.

[Slide.]

For acute exacerbation of chronic bronchitis, we had two studies that were submitted with the original NDA, Study 3003 and 3007, and one study that was in the resubmission, Study 3013.

If you notice the color scheme, I added as a convention for the rest of the slides, so you will know, the green studies are studies that were submitted with the original NDA in February of 2000 and reviewed prior to the first Advisory Committee in April of 2001, whereas, the studies in yellow will be those studies that were submitted as part of later submissions just so that you can understand a little bit of the timeline and the information that we had at about what time.

[Slide.]

With regards to the studies for acute

exacerbation of chronic bronchitis, the comparators are shown. amoxicillin/clavulanate and cefuroxime axetil were used as comparators in the studies in the original NDA, and clarithromycin was used as the comparator in the study in the resubmission.

All of these studies are non-inferiority studies. They were designed to compare clinical outcome at the test of cure visit for those patients with telithromycin versus those patients with comparator.

[Slide.]

So this study shows the results in the per- protocol and the MITT populations showing the clinical cure rates of the test of cure visit for patients treated with telithromycin, patients treated with comparator, and the 95 percent confidence intervals around the difference in cure rates between the two groups.

[Slide.]

Now, there were also pathogen analyses that were done. Those are available to you in your briefing package. Briefly, I wanted to mention the

reason we had an additional study submitted as part of the resubmission in 2002 was because of concerns that were raised as part of the Advisory Committee evaluation of the results with regard to outcomes for patients with AECB due to Haemophilus influenzae.

What is shown is the numbers that we had for the original NDA in telithromycin patients with bacteriologic success for patients with AECB due to Haemophilus influenzae was 15 out of 25, which is 60 percent, versus what was seen for comparators.

So the resubmission study was in essence to provide us with some more clinical experience in patients with AECB due to Haemophilus influenzae. The results of the bacteriologic success rates for patients with AECB due to H. flu in the resubmission are shown.

[Slide.]

For acute bacterial sinusitis, there were three studies that were provided within the first review cycle. There were no new acute bacterial sinusitis studies provided in either of the

resubmissions, so all of the data that we had were part of the original NDA.

Study 3002 is a comparative study of telithromycin treatment without an active control arm, so the study was designed around looking at telithromycin given as 800 mg once a day for 5 days versus 10 days.

Study 3005 was a comparative study whose diagnosis was based on clinical grounds and looked at clinical outcomes at the test of cure visit. Amoxicillin-clavulanic acid was used as the comparator.

Study 3011 was a study of telithromycin compared to cefuroxime axetil 250 mg bid for 10 days. This study included baseline microbiologic diagnosis, as well as diagnosis based on clinical criteria.

Again, all of these studies are around the same design of non-inferiority especially Study 3005 and Study 3011 where you are talking about non-inferiority against an active comparator, and they looked at clinical cure rates at the test of

cure visit.

[Slide.]

That is what is shown in the results here for these slides. Again, I remind you that what is shown in the comparator column for Study 3002 is the results of patients who were treated with telithromycin for 10 days.

[Slide.]

Again, the pathogen analyses are available in the briefing package. One thing I would like to point out was the information that we had at the time that a concern was expressed with regards to the outcomes for patients with AECB due to H. flu.

What we saw in the ABS studies was comparable H. influenzae cure rates for patients in telithromycin and cefuroxime treatment arms, so you had roughly 80 percent cure rates depending on what you are looking at, the per- protocol or MITT analysis for both treatment groups.

The briefing package also includes the information on outcomes for penicillin and erythromycin-resistant strains of Strep pneumoniae

and acute bacterial sinusitis. But I would make the point that at the end, no specific claim for ABS due to MDRSP was made and that is because of the fact that what we had was at that time knowledge that there was a small treatment effect, so what the contribution of MDRSP in this disease entity was, was unclear to us.

[Slide.]

Moving on to community-acquired pneumonia, what I am going to show are the results for the original NDA studies. There were three comparator trials that were done, Study 3001 comparing telithromycin to amoxicillin, 3006 using clarithromycin as a comparator, and Study 3009 using trovafloxacin as a comparator. As was noted earlier, the study with trovafloxacin was discontinued early because of concerns with regard to the safety of trovafloxacin.

There were also three open label studies that were provided for additional experience with patients with community-acquired pneumonia due to pathogens identified as part of the open label

studies.

[Slide.]

What is shown here now are the overall results for the three comparative studies and the three open label studies. The three open label studies don't have any information with regard to comparator or confidence intervals.

With regard to the numbers that you are seeing here, for Studies 3009, you will notice that there is a larger confidence interval. Part of that is related to the fact that you are talking about a study that was stopped early, so the number of patients is smaller.

Also, of interest is for Study 3001, the study that used amoxicillin as a comparator, the lower bounds of the 95 percent confidence intervals in the per protocol and the MITT analyses are roughly 2 percent and a half a percent respectively.

[Slide.]

Also, information that we had that we looked at, at the time of the original NCA

submission in the first Advisory Committee was information on subgroup analyses looking at patients specifically with bacteremia or subgrouping patients by Fine score.

The per-protocol is given there as sort of a comparison information to the subgroup analyses.

For patients with Strep pneumoniae bacteremia, what was seen was success in clinical cure rates at the test of cure visit of 43 out of 47, 91.5 percent.

You can also see the results of clinical cure rates in the telithromycin group by Fine score. Again, these are telithromycin cure rates and this incorporates information on telithromycin-treated patients from both the comparative studies, as well as the open label studies.

[Slide.]

Turning now to the multidrug resistant Strep pneumoniae in CAP, part of what you heard earlier was that part of what we were looking for after the first Advisory Committee was additional

experience with regard to patients with penicillin and erythromycin resistant strains of Strep pneumoniae.

In order to provide that information, the sponsor submitted two studies, a comparative study of telithromycin for 5 or 7 days, so that was two separate treatment arms compared to clarithromycin given for 10 days.

There was also an additional open label study of telithromycin for 7 days provided as part of the submission. The FDA's resubmission analyses focused on looking at the outcomes for patients with resistant pathogens.

[Slide.]

So I want to walk you through this table a little bit. What this is, is a table of patients with CAP due to MDRSP and all of the numbers in the table represent patients who are treated with telithromycin. This is information that is coming from both the comparator trials, as well as the open label studies.

For patients with community-acquired

pneumonia due to MDRSP, each of the rows show what the outcomes were for patients who had an organism that showed resistance to the antimicrobial listed.

The first column shows the antimicrobial. The second column shows the results for telithromycin-treated patients in the MITT group, and the third column shows the result for telithromycin-treated patients in the per-protocol analyses.

Each row may include patients that are in the next row. But, when we are talking about these results overall for patients with community-acquired pneumonia due to MDRSP, what we were seeing were comparable results to what was seen for patients with Strep pneumoniae overall.

I would note here for the line for erythromycin, for the outcomes that were seen for patients with community-acquired pneumonia due to erythromycin-resistant strains, their numbers here include 8 subjects who had an organism, Strep pneumoniae organism, that was resistant to erythromycin alone. But what I wanted to show here

was that for telithromycin where we would be most concerned about the potential for decreased activity would be in those patients who had a macrolide-resistant strain and what we are seeing are the numbers that are shown.

[Slide.]

Moving on now to pre-approval safety, as we were looking at the application initially, we had a lot of information, so this is a ketolide. It's a new chemical entity but it was known to be related to the macrolide class of antibiotics, so we were looking for specific adverse effects that we knew were associated with a macrolide class.

We did have animal toxicology studies that provided us with some information about hepatic, as well as potential cardiac adverse effects on QT prolongation.

Other information that we had from clinical pharmacology studies is that the drug is known to be a CYP3A4 and a CYP2D6 substrate, as well as being a strong CYP3A4 inhibitor, so the potential for drug interactions was also something

that we investigated as part of the clinical studies that were done.

There was also information from Phase I studies, liver function test increases noted in patients in the Phase I trials.

[Slide.]

Moving on to the data that we had for safety in Phase III trials. This information was already displayed by the sponsor in their analyses. What is shown here are the patients in the comparative trials who received either telithromycin or comparator.

You will notice that the number of patients for the telithromycin-treated group is larger, and that is because of the fact that some of the studies were two-arm or three-arm trials where there were two separate arms of telithromycin that were included.

Overall, what we are seeing is comparable rates of common, less serious adverse events. Of course, this doesn't tell us necessarily a lot of information about more serious rare adverse effects

of the drug.

[Slide.]

Moving on to focus on specific adverse effects of interest. I will start out with visual adverse effects.

As noted earlier, these visual effects were first recognized as part of Phase III trials. What were seen were visual adverse event rates of 1.1 percent for Ketek-treated patients versus 0.3 percent roughly for the comparator-treated patients.

What was reported was visual blurring occurring more in females than in males, and occurring more in patients in the younger age group. It was actually noted mainly within the trials of Strep pharyngitis.

Also, of interest was an analysis that was done where we looked at patients who had received a CYP3A4 inhibitor as part of their treatment while in the clinical trials versus those who didn't, and you saw more visual effects reported for those patients who had received a CYP3A4 inhibitor.

Now, what was reported was mostly some mild effects on blurred vision. Some patients discontinued treatment, others continued their treatment. Most of the reports of visual effects occurred with the first or second dose but it was noted in patients later on in some cases.

Because of these concerns about what these visual effects were, as part of the resubmission the sponsor conducted some mechanistic studies. Their studies did confirm that what we were seeing was a dose response.

The mechanistic studies are described in Appendix D of your briefing document. Briefly, what they involved was giving patients a supertherapeutic dose of telithromycin, so rather than the regular 800 mg dose, patients received a 2,400 mg dose. As was described earlier, what it appeared to be related to is an effect on accommodation and release of accommodation although the mechanism isn't thoroughly elucidated.

[Slide.]

Moving on to cardiac adverse events, QT

prolongation was something that was being identified as a concern, not only with Ketek but with other antimicrobials at around the time of the submission of this original NDA.

What was noted in the Phase III trials results was an on-therapy increase in QTc and what I am showing you there are the numbers for QTc using Bazett's and Fridericia's formulas.

There was a careful review of cardiac adverse events as part of the Phase III trials. What we were trying to evaluate was the potential for QT prolongation leading to problems with patients especially those who had drug interactions.

So, as part of the resubmission, there were additional Phase I studies that provided us more information about QTc prolongation. Specifically, the study that Dr. Soreth noted as the "stack the deck" study involved patients who were elderly, who had some degrees of renal impairment, and were also given a CYP3A4 inhibitor ketoconazole in order to further evaluate what

happened with QTc prolongation in patients who are expected to have higher serum concentration of ketolide because of this combined effect.

What ended up being noted is that there is probably a small effect on QT prolongation comparable to clarithromycin in those studies. Again, there will be some mention of QTc prolongation as part of tomorrow morning's session.

[Slide.]

With regard to hepatic adverse events, there were some LFT increases noted in the Phase III trials and some liver ladders are provided as part of Appendix B in your briefing document.

Of concern in the original NDA database were serious hepatic adverse events noted for two patients, a 76-year-old female with CAP, and a 50-year-old Finnish man that was the topic of discussion at both the first and second Advisory Committees, as had already been mentioned by the sponsor.

Because of the concerns about the potential for serious hepatic adverse events noted

within the NDA database, this is part of what led to the overall design of Study 3014 in order to try and investigate whether we were going to see common occurrence of serious hepatic adverse events. You have heard some discussion about the concerns with regard to Study 3014.

[Slide.]

I am going to move on to the information that we had for foreign postmarketing. This information was submitted to us as of October of 2003, I believe.

The information that we had was on approximately 3.7 million exposures ex U.S. as of January 2003, most of the information coming from France and Germany but also from other countries within the European Union, within Latin America, and the International information from French overseas areas.

There was information that was provided on a total of 2,345 adverse event reports in 932 patients. Of course, I am not going to be able to go over all of the detailed information on the

foreign postmarketing, so I am going to focus on information on visual, hepatic and myasthenia gravis.

Appendix C of your briefing document had provided selected sections of the overall review of this foreign postmarketing information highlighting those specific areas of concern.

[Slide.]

The information that we had on the foreign postmarketing, visual adverse events were reported as 415 adverse event reports occurring in 315 patients. This accounted for 33 percent of all patients with adverse events reported in postmarketing.

Serious visual adverse events were 101 reports in 66 patients. What was noted with regard to the counts for these adverse event reports were that they occurred more in females than they did in males and the counts were greater for those patients less than 40 in comparison to those 40 to 55, or those older than 55. That is consistent with the information that we had from the NDA

database.

In terms of what was being described as severe visual adverse events, these were adverse events that were interfering with individual's activities of daily living, patients reporting blindness for a period of time, not being able to see.

There was a particularly memorable report of an adolescent female who had received the drug, who was complaining that she couldn't see herself in the mirror.

What we know about the data from these foreign postmarketing reports was that most of the reports included patients that recovered, although there was a proportion of patients where the information indicated that the event was either ongoing or something as sequelae was reported. But we have limited information in these passive reports to make a determination on what those prolonged effects are.

[Slide.]

With regards to hepatic AE, there were 90

reports occurring in 43 patients, 24 were female, 16 male and the rest unknown. The report in Appendix C sort of details the information that we had about patterns of liver injury, again most were unclear. Of those that we had information with regard to several liver function tests, there appeared to be more to be more patients with cholestatic versus cytolytic injury but we have limited information on which to make any conclusions with regard to causality.

In total, there was only one death that was reported as part of this foreign postmarketing exposure but this individual had multiple confounding factors reported including hepatitis A, Q fever and high-dose acetaminophen.

Again, this is the information that we had at the time of approval. You are going to hear later on this afternoon more information about domestic cases of hepatic adverse events.

[Slide.]

Also, noted in foreign postmarketing were exacerbations in myasthenia gravis. We didn't have

any information on the occurrence of exacerbations in myasthenia gravis within the setting of the controlled clinical trials. But that is not surprising given the rarity of myasthenia gravis itself.

What were identified were 13 patients assessed by the medical officer as having likely cases and 6 patients having probable cases of exacerbation of myasthenia gravis.

The symptoms that were reported varied from ptosis and weakness to respiratory failure including one patient who was reported as a death.

[Slide.]

In 2004, on April 1st, we approved the use of telithromycin tablets, 400 mg tablets, for the treatment of community-acquired pneumonia including MDRSP, patients with acute bacterial sinusitis and acute exacerbations of chronic bronchitis.

Given the information that we knew from the controlled clinical trials, as well as the foreign postmarketing, the label included warnings for QT effects, warnings for myasthenia gravis

exacerbation and C. difficile colitis.

There was also information in the Precaution Section with regard to hepatic dysfunction, with regard to visual adverse events including some precautions with regard to driving and, of course, information on the drug interactions that occurred.

[Slide.]

So, with the approval, we go into the period of U.S. postmarketing. There was continued monitoring for adverse effects including a reassessment of all the adverse effects that had occurred at approximately a one-year time point.

As part of the postmarketing activities, there was also approval of a 300 mg tablet formulation for patients with severe renal impairment, because part of the information that we got from the "stack-the-deck" study was that a 600 mg dose as opposed to the usual 800 mg dose for most adults, appeared to be more appropriate for patients with severe renal impairment.

There was also a labeling supplement that

was submitted and the review of that labeling supplement is provided in Appendix E of your briefing document. This added precautions particularly of note with syncope usually associated with vagal syndrome.

This was added as a precaution because of the fact that these reports involved postmarketing adverse-event reports mainly coming from Japan. But one of the cases included the occurrence of a car accident, so again the concern about the potential effect of the drug on patients who would be driving.

There were a total of 56 reports in the syncope/loss of consciousness preferred terms as of July 1, 2004, after the medical officer review of these cases, this was reduced to 11 cases that are thought to be potentially associated with the effect of telithromycin on treatment, and that is what led to the labeling supplement.

You will hear more discussion later on in tomorrow's session about syncope and loss of consciousness reported in postmarketing and

domestic cases in the U.S.

There was also not listed on the slide an additional labeling supplement that came in, in June of 2006, to add information with regard to hepatic adverse events and to strengthen the information with regard to myasthenia gravis that will be discussed later on in these sessions.

That ends my presentation.

DR. EDWARDS: Thank you very much.

We now have time for questions from the Committee. We are actually just a little bit ahead of time. I am planning to break at 10:55 as scheduled, so let me open the activity up to questions from the Committee.

Yes, Mr. Levin.

Committee Questions

MR. LEVIN: Two questions of FDA. One, is there more information in the discussion about the regulatory briefing meeting of February 19, 2003, is there more discussion that is available to us of what went on in that meeting that led to the decision to rely on postmarketing data from other

countries as a substitute for a corrupted or failed safety trial that was asked for as part of the approvability letter in the beginning of this process?

We had a process where the Agency and the Advisory Committee asked for further study, problems with that study, and a decision was made to accept postmarketing ADE information as a substitute for that study because of the problems with that study. That is the first question.

Related to that is under what circumstances does FACA permit a closed advisory committee meeting, which apparently occurred to discuss that data after the public meeting?

DR. COX: The first question with regards to the foreign postmarketing data--I don't recall the discussions that took place during regulatory briefing but we do look at postmarketing data that is available for products that are out there and marketed, something that is required to be submitted, so that information can provide very helpful information in looking at adverse events

that may be occurring at very, very low frequencies.

Just looking at other instances of foreign postmarketing data and their use, they have in the past been informative for other products that have had problems with hepatic toxicity. So, in the past, that type of information has disclosed signals of toxicities, so foreign data can be helpful.

Interesting, too, is in the discussions today, too, we have heard about myasthenia gravis and the source of the information that was included in the label with regards to exacerbations of myasthenia gravis was something that came from the foreign postmarketing data that was available to us.

DR. J. JENKINS: Let me add a little bit to that. I am not an attorney, so I am not going to give you a legal answer on the FACA, but we occasionally do have closed sessions of advisory committees to discuss primarily drug development plans that are still commercial confidential

information, so they might be during the IND phase where we are seeking advice from the Committee on development of studies or things of that nature that are still during the IND phase, that they are not approval discussions, so we don't have closed meetings to talk about approval decisions for applications.

I think it was at that meeting, as Dr. Soreth mentioned, that the Committee was updated on the fact that we had not followed their advice from the January meeting and it was given as a courtesy update about the ongoing investigations about the 3014 study.

Another point to make about the hepatic adverse events and the controlled clinical trial versus postmarketing surveillance data, we require companies to submit all available postmarketing safety data when they submit NDAs to the FDA, so if the drug has been approved in other countries, we expect them to submit those data to us as part of the safety package and we routinely review that for approval.

There was a time in history when most drugs were approved outside of the United States before they were approved here, where we probably utilized that data more than we have in recent years where we tended to approve the drugs either first or about the same time that they have been approved in other countries. But it is a requirement that that data be submitted.

One other point to keep in mind is that the 3014 study was designed to try to rule out a 1 in 4,000 risk of serious hepatic dysfunction. That was based on the one case that was seen in the original NDA database.

So, that was what was being considered when we were having the internal regulatory briefing. The study was powered to look for a risk of 1 in 4,000, and how much comfort could you take from, say, a 4 million exposure database from postmarketing experience and assessing what the potential risk for serious adverse reactions might be. So, that was the discussion that was held.

DR. EDWARDS: Dr. Follmann.

DR. FOLLMANN: So part of our charge is to look at overall risk and benefit. We have heard some discussion today about MDRSP, resistant strains of pathogens, and Ketek is, in fact, labeled for MDRSP.

I was interested in the evidence that was used to make a determination. I don't know if this is a question for the sponsor or the FDA but I think the sponsor had a slide that might make it easier for me to make my point.

This was Dr. Edelberg's slide 3-18, which I believe was a lumped analysis of both the randomized, controlled studies in CAP, as well as three uncontrolled studies in CAP. I just want to walk through sort of the thinking that resulted in the label for MDRSP.

It seems what was going on here, they had three randomized comparative studies and they passed the non-inferiority margin for that. But there wasn't sufficient evidence to grant a label for MDRSP so they enriched the database by doing three subsequent studies focused on resistant

strains.

You see the data displayed here. That is why you have this disparity in the numbers. To me, it would have been more direct and stronger evidence if there had been a randomized study of superiority or even non-inferiority that focused on these resistant strains.

What we have here is more overall it was equivalent in a large body of pathogens and then, without a comparator, we focused on studies where there are these resistant pathogens.

We note, somewhat informally I guess, that the cure rates are similar for the resistant pathogens in these non-controlled studies and, therefore, we conclude it's effective clinically against MDRSP.

If you sort of twist this around, if you would say this isn't really fair--but if you would twist this around and do an equivalence of the data here, you would find that the comparator meets the overall non-inferiority margin, so with the same kind of thinking, if those numbers were larger, and

the rates were around 80, 90 percent, maybe the comparator could conclude that they were effective, therefore, MDRSP.

The point I am trying to make here, and I would like some discussion on it, is it seems like the evidence to make this conclusion of MDRSP is certainly not as strong as would you would have had if you had a comparative study that focused on this question.

DR. COX: With regards to the resistance claims for Streptococcus pneumoniae, generally, the approach here has been one to look at how the drug performs in treatment of Streptococcus pneumoniae in general, so those susceptible and resistant strains.

Then, looking also at cases where there is bacteremia or in situations where there is more severe disease. Then, looking sort of at the top of the pyramid would be to look at those strains where there is, in fact, resistance present.

What we are really doing here is looking in essence at one of the organisms within the

overall indication, so it is not something that has been statistically powered.

You will notice within the indication, there is a variety of strains, and this is, in essence, a group within one of those organisms. We look at the specific cure rates for each of the particular pathogens within the overall community-acquired pneumonia study, and that would be derived from the microbiologically evaluable subpopulation.

It is more looking at how the drug is faring in a representative group of organisms which are resistant to drugs commonly used to treat Streptococcus pneumoniae, much more in the way that we are looking at adding particular bacterium to the list than we are a separate indication.

Another thing to keep in mind, too, is that the particular comparator that is cited there, the particular strain of Streptococcus pneumoniae, the multidrug resistant strain, may be susceptible to the comparator, too, so it is not necessarily true that the comparator would be a drug to which

the organism is resistant. That may help put that in a little more context.

DR. FOLLMANN: When you say the comparator might not be resistant to the organisms, that is based on the assay or the in vitro test. I don't really know what that means necessarily.

What would really be definitive for me would be to look at the clinical cure rates, not sort of based on if you classified these organisms and then looked at clinical cure rates, this is sort of making the leap of faith that the in vitro assay is really a good surrogate for discriminating a comparator wouldn't work and Ketek would work.

DR. COX: And the comparator, too, may actually be multiple agents, they are all pooled together. If you were to do a statistically powered study to show superiority, then, that would be stronger evidence. But I think we are looking at this more in the context of the types of information that we would look to add an organism within the overall indication and also to gain some experience with the types of patients that may have

resistant strains to Streptococcus pneumoniae to make sure that there aren't clinical differences or other factors that may be contributing to a patient population that may be more difficult to treat and making sure that the agent still preserves its efficacy there, and that the cure rates are similar to what we are seeing in the overall patient population including the larger body of patients with susceptible strains to pneumococcus.

DR. HILTON: I think Dr. Alexander's Slide 13 also addresses this issue. On that, I was kind of concerned about the difference in the rates for the modified intention-to-treat population versus the per-protocol.

The per-protocol rates look pretty excellent but I am very concerned about the substantial reduction in the modified intention-to-treat group where the denominators are larger.

DR. ALEXANDER: Again, looking at what we are talking about, most of the numbers that you had seen in the rest of the presentation are actually

related to the per-protocol population, even the information in the briefing packet, when we are looking at the MITT populations and the MITT rates due to Strep pneumoniae, we are also seeing what are lower cure rates in the MITT population for patients with community-acquired pneumonia due to Strep pneumoniae, so that is something that we typically see in terms of an overall dropoff.

If you look at the outcomes for community-acquired pneumonia, for the primary endpoint, you will see differences between what were the overall outcomes in terms of the per-protocol group and the MITT group, as well.

We are looking at the comparisons for the MITT groups, as well as for the per-protocol.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: This is a particularly important point given that we have heard that a lot of patients, not in CAP but in some of these other conditions, will respond without any treatment, and so, if it's only 75 percent responding--this is different because this is CAP--but in some of these

less serious conditions, if it's only 75 percent, perhaps a placebo response rate would be close to that.

DR. EDWARDS: Dr. Norden.

DR. NORDEN: Can I ask John Bartlett a question?

DR. EDWARDS: Yes.

DR. NORDEN: John, I thought that was really an excellent presentation. The question I had for you is really to do with AECB, because I think it is going to come up later when we try to look at the risk-benefits.

The only study that you were able to cite that showed a real benefit for antibiotics that you would feel comfortable with was the Lancet paper, which was certainly severe cases, and probably not what most of us associate with AECB.

I just want to be sure that that is your interpretation also, because I think it is not the kind of thing that most patients are getting treated with Ketek or moxifloxacin for anyway.

DR. BARTLETT: Yes, Carl, you are right.

That was a study in which patients were admitted to an Intensive Care Unit to be placed on a ventilator, and was certainly unique in that way. The difference was big, though, 4 percent versus 22 percent for death.

DR. EDWARDS: John, before you sit down, I wanted to ask a question also. If I interpreted your comments correctly, I believe you and Dr. Low may have a little bit different viewpoints on the significance of macrolide resistance. I wonder if you could elaborate on that.

DR. BARTLETT: I made two points about macrolides. One is that they seem to do better in vivo than they would appear to do in vitro. I don't think that is incompatible with what Don said. I think what he said was that there is a higher rate of failure with macrolides.

I think my point was that there is a big difference between the in vitro and in vivo response, that doesn't seem to indicate that the in vitro data has been a very good marker.

The second point I was making is they seem

to do something with pneumococcal bacteremia that we have been puzzled by. But, of course, it may be that the macrolides have some anti-inflammatory effect that accounts for some of the activity they have shown in various infections.

I am not sure what Don and I said is incompatible. I think we were sort of saying that there is a high rate of in vitro resistance, and I am saying that it looks better than it does in a test tube, and he is saying that, well, there are still more failures in that group.

So I think they are probably compatible. But we are sort of looking at it half-full or half-empty.

DR. EDWARDS: Dr. Low, would you like to comment?

DR. LOW: I agree and these are really difficult studies to carry out especially after drugs have been approved. I think that Dr. Lonks will also make some comments about macrolide failures and resistance in a subsequent presentation.

DR. EDWARDS: Thank you.

MS. SHAPIRO: This may be addressed later and, if so, that's fine, but I am wondering if we could get more information about the requirements and the practice of adverse event reporting in foreign countries and how representative those reports are projected to be in terms of the universe.

DR. EDWARDS: I believe we are going to discuss that in some detail. Is that not correct, Dr. Dal Pan?

DR. DAL PAN: What we are going to hear is we are going to hear from the European Medicines Agency later about their 5-year review of telithromycin. We could perhaps ask the representative to talk about how postmarketing reports are handled at least in the European Union or in the country which he is representing.

If you wish, I could talk about what spontaneous reporting actually is in the United States, as well.

DR. EDWARDS: Are there any other

questions at this time?

[No response.]

DR. EDWARDS: We will break until 10:55. Thank you.

[Break.]

DR. EDWARDS: At this time, I would like to turn the meeting over to Dr. Stephen Jenkins, who is going to direct the sponsor's presentations for the next portion.

Dr. Jenkins.

Sponsor Presentation

Postapproval

Microbiologic Surveillance

Stephen G. Jenkins, Ph.D.

DR. S. JENKINS: Good morning. Thank you for the opportunity to present today. I apologize upfront, I have a viral syndrome and my voice isn't carrying particularly well, but that is a condition for which antibiotics do not play a role.

[Slide.]

I have been asked today to speak on the postapproval microbiology studies that have been

conducted with telithromycin or Ketek.

[Slide.]

The objectives of the various studies that have been conducted basically attempt to look at follow-up data on the in vitro activity of this compound against the key respiratory pathogens, focusing on Streptococcus pneumoniae, the organism that has already been described by Drs. Bartlett and Low that is the most important pathogen, and community onset respiratory infections, but also focusing on Haemophilus influenzae while collecting data on other organisms, as well, including Staphylococcus aureus, Streptococcus pyogenes, Legionella pneumophila and other organisms encountered in this setting, and then to compare the findings for telithromycin to other antimicrobial agents that are used for treatment of these respiratory tract infections.

Secondly, to monitor the epidemiology of antimicrobial resistance in the pneumococcus, the trends of that resistance both in terms of the phenotypes, the MICs of these organisms and the

genotypes, the molecular characterization of the genes that code for that resistance and, finally, to assess the impact of the heptavalent Prevnar vaccine on the various serotypes of pneumococcus that we are encountering in these infections.

[Slide.]

Now, to do this, most of the studies have been from a program called PROTEKT. This is a very large international surveillance program that collects isolates from patients with well-characterized respiratory tract infections and then looks at them in terms of their in vitro susceptibility. Laboratories are recruited to participate in the study and they collect consecutive isolates from patients at their various institutions.

Now, there are two large programs I am going to share information with you this morning. The first is the Global PROTEKT program which has been ongoing since 1999, prior to the launch of telithromycin in Europe.

In this study, 35 countries are

represented and 116 sites participate in these analyses. All of the work is conducted at one central laboratory called GR Micro in London, where they do the susceptibility testing itself, the genotyping of these organisms, and serotype the various pathogens that are submitted.

The PROTEKT U.S. program has been going since 2000, 191 sites participate in this program. They are in the fifth year of the study. The central laboratory that test these organisms in the United States is the CMI laboratory in Wilson, Oregon, where the MIC testing is performed and then all of the isolates are transferred to GR Micro for consistency purposes for the genotyping and serotyping studies.

[Slide.]

Let's focus first on the PROTEKT US program, looking a little bit at the epidemiology by geographic area in the United States and the in vitro activity of telithromycin against the pneumococcus for the overall population by age group and by genotype and then, at the end, looking

at some information on Haemophilus influenzae, the second most commonly encountered pathogen in these infections.

[Slide.]

This looks at the data in Year 5, the most recent year for which we have information on the prevalence of antimicrobial resistance by region.

I think it is interesting that the Northwestern and Southwestern states clearly have lower rates of antimicrobial resistance than other parts of the country, such as North Central, South Central and Southeastern states.

That having been said, the macrolide resistance rates and multidrug resistance rates clearly are bothersome. The lowest rates we are seeing in any region in the United States is currently 22 percent.

[Slide.]

Here, we are looking at the in vitro activity of a variety of antimicrobial agents again against Streptococcus pneumoniae. The overall population that was studied in the fifth year of

the study included about 9,500 isolates of Streptococcus pneumoniae.

The resistance rate for telithromycin in this study was 0.1 percent. By comparison, the resistance rate to the macrolides, azithromycin being a representative of that class, is currently around 31 percent, Augmentin overall about 5.5 percent, cefuroxime axetil is a representative of the second-generation cephalosporins at about 20 percent, and levofloxacin as an example of a fluoroquinolone at about 1 percent.

If you then cut the data into subsets where you have macrolide-resistant organisms and multidrug-resistant organisms, some very interesting things can be seen.

First of all, the resistance rates for telithromycin for all of these categories remains considerably below 1 percent.

For penicillin-resistant strains, interestingly, over three-quarters of these organisms are concomitantly resistant to the macrolides, Augmentin about 32 percent are

resistant, essentially, 100 percent are then resistant to the second-generation cephalosporins, and you notice that the resistance rates to the fluoroquinolones creep up a little bit.

Even if you look at multidrug-resistant organisms, resistant to five or more classes of antimicrobial agents, the activity of telithromycin remains high, only about a half a percent are resistant as compared to essentially 100 percent resistance for azithromycin, 55 percent for amoxicillin-clavulanic acid, 100 percent for the second-generation cephalosporins and about 2 percent for the fluoroquinolones.

[Slide.]

I think another way to look at the data is over time. So we are now looking at resistance rates to these various antimicrobial agents over the 4-year period for which we have data. It does sort of track some of the comments that have been made by both Drs. Bartlett and Low.

If you take a look, for instance, penicillin resistance rates have actually declined

from 2000 about 26 percent down to a rate of about 17.5 percent today. I think this is a direct impact of the Prevnar vaccine.

Interestingly, though, we have seen an increase in the proportion of pneumococcus that are intermediate in their susceptibility to penicillin.

Finally, macrolide resistance really has not been impacted by the introduction of the Prevnar vaccine. It has held steady at about 31 percent during this entire period of time.

[Slide.]

Here again we are looking at Year 5 but now cutting the data by age group, and again no surprise. If you look at isolates recovered from children less that 2 years of age, almost 50 percent of those organisms are resistant to the macrolides, whereas, the rates to the fluoroquinolones are very low as would be expected since this class of compound is not used for treatment of pediatric infections of this type.

By comparison, if you look at isolates from patients more than 64 years of age, the

macrolide resistance rates are somewhat lower but the fluoroquinolone resistance rates are higher, again as would be expected.

[Slide.]

This slide looks at the resistance rates to telithromycin and the macrolides based on the genotype of resistance. I will have to take one second to explain this.

There are actually two broad categories of macrolide resistance. The first encoded for a gene called erm(B) results in blocking of the binding site, so literally, the antimicrobial agent cannot bind.

The MICs, as you can see, are very high, which essentially states there is no activity of these compounds at all in vitro against these organisms.

By comparison, if you take a look at the activity of telithromycin against these strains that have methylation of their ribosome, the resistance rate is only 0.6 percent.

The second broad category of resistance to

the macrolides is encoded for by a gene called mef. Here, we have a situation where as the antibiotic comes into the bacterial cell, it is pumped right back out again, so this is an efflux mechanism.

Again, about 0.1 percent of these strains are resistant to telithromycin and essentially 100 percent resistant to the macrolides.

Finally, of increasing concern is the growing proportion of pneumococcus that now have both genes, so they are not only blocking their binding site, there is also an efflux mechanism coming into play, very, very high levels of resistance to the macrolides, 0.7 percent resistance to telithromycin.

[Slide.]

This looks at the PROTEKT Years 1 through 5 in the increase in the proportion of pneumococcus that actually now express both mechanisms of macrolide resistance.

You can see that the largest increase in these strains is in the 0 to 2-year-old age group, again a function of Prevnar, the emergence of a

serotype called 19A that happens to have both genes, both mechanisms of resistance. Other age groups, the increase has been smaller but, clearly, is also occurring.

[Slide.]

This slide looks at the increase in resistance to another class of compounds commonly used for community-acquired respiratory infections, that being amoxicillin-clavulanic acid, specifically, amongst those organisms increasing in number that have both mechanisms of macrolide resistance.

The point I am trying to make here is we have gone from about 30 percent of the isolates that have both mechanisms of resistance, resistant concomitantly to amoxicillin-clavulanic acid all the way up to about 69 percent today.

[Slide.]

Likewise, if you take a look at the resistance rates over time amongst the serotype 19A isolates that are increasing in frequency in children 0 to 2 years of age, penicillin resistance

rates have climbed from 22 to 46 percent, macrolide resistance rates from 56 to 69 percent, and amoxicillin-clavulanic acid resistance rates from 10 to 33 percent.

If you take a look at the resistance rates with telithromycin, they remain considerably below 1 percent, currently at about 0.3 percent.

[Slide.]

This slide looks at the global data, are we seeing any differences globally where the compound has been used to a much larger extent than in the United States?

The global data indicate that about 19 percent are resistant to penicillin, 17.5 percent overall in the United States, no big difference. Macrolide resistance from the global program, about 35 percent as compared to 31 percent in the United States, no different. Similar figures likewise for multidrug resistance.

[Slide.]

I think one question that came to my mind in looking at and evaluating this data is in all of

these studies, laboratories drop out over time. You can't recruit the same laboratories year after year after year, and could we have some type of skewing of the data as one laboratory drops out and another is recruited to participate in the program.

So now we have looked at the data over the entire global program for all laboratories, those that were common throughout the five years of the program and, for those where telithromycin has been largely marketed, those countries specifically being Belgium, France, Germany, Italy, Spain and Turkey, where over 13 million patients have now received a course of therapy.

The important point here is there really is no difference in the resistance rates to telithromycin in each of these three subgroups.

[Slide.]

Finally, one other organism that is clearly important in these respiratory infections, Haemophilus influenzae, telithromycin resistance rates are currently running about 0.6 percent, very similar, interestingly, to the macrolides, to

amoxicillin-clavulanic acid, cefuroxime, and somewhat higher than the fluoroquinolones.

The global program, we have actually seen an increase in resistance rates to amoxicillin-clavulanic acid and cefuroxime axetil to beta-lactam class antibiotics over the five-year period of time. Why this is interesting is it signals a new type of resistance that is evolving called beta-lactamase-negative ampicillin resistance among strains of Haemophilus influenzae.

[Slide.]

So, in summary, telithromycin's activity against the pneumococcus remains high in the United States and globally, currently, about 0.1 percent.

So far, no signal of increased resistance to the compound, no indication of clonal spread of resistance to the compound.

Telithromycin maintains its activity against the increasingly common, highly antibiotic-resistant strains of pneumococcus, both the 19A serotype evolving in the United States, and those strains that have both mechanisms of

macrolide resistance and its activity has remained stable against the second most common pathogen in this setting, Haemophilus influenzae.

Thank you very much.

DR. EDWARDS: Thank you.

Dr. Lonks.

Clinical Importance of Ery-resistant S. pneumoniae

John R. Lonks, M.D.

DR. LONKS: Ladies and gentlemen, thank you for the opportunity to present some of the clinical importance.

As a clinician, when I was looking at Dr. Jenkins' slide with resistance, there are different classes of drugs used for pneumococcal infection, the macrolides, penicillin, fluoroquinolones and now the question of the use of telithromycin in this field of infection.

However, the highest rate of resistance that you saw, the top bar was macrolide resistance, so the in vitro rate is very high. What does this really mean in patients, and that is what I am going to try to address.

[Slide.]

The data that I am going to present is data that includes failures--and I will describe failures in a minute--that include treatment failures to isolates that have all kinds of resistance of mechanisms, whether the methylase gene or the efflux pump and, additionally, some of the data includes Dr. Low's study where the MICs to erythromycin were as low a 1 mcg/ml.

These rates continue to increase both in vitro and I will show you that the rates of treatment failures are also increasing in the clinic.

[Slide.]

When I say "treatment failure," I am specifically meaning that a patient is being treated with a macrolide antibiotic, usually erythromycin, clarithromycin, or azithromycin, while taking the therapy that either are not responding to drug or getting worse and, in most cases, they are presenting to the emergency room because of this clinical worsening. Blood cultures

are obtained and the blood cultures are growing pneumococci.

This is also a mark of the severity of disease. People with pneumococci in their blood are much more sick than those who do not.

When the data starts off, I will show you on the slide in a minute, we go from the progression of case reports, which because the phenomena was very rare, to case series, which some are population-based, and then the population-based case control studies are looking at failures.

[Slide.]

I will walk you through this slide. On the bottom is the beginning or actually beginning of the macrolide era is in the 1950s. Data from the 1960s are not shown here. There was zero resistance to erythromycin.

If you look at the resistance rates for erythromycin at the open circles, I have chosen three studies done by the CDC.

In the first study, you can see most of the years, the rates are under 1 percent, one year

the rate was 3 percent. In the early 1990s, the rates went up a little bit higher, the mid-nineties even higher, and more recently we see even higher rates of erythromycin.

Additionally, during the same period now, I have the macrolide failures. Way back here there were some rare treatment failures in which pneumococci was isolated from either lung tissue or blood. But these were rare phenomena, however, as macrolide use went up and resistance went up, the number of case reports--and this is either by the year of occurrence or the year reported depending on what was available in the literature--you can see that there was an increase.

Some may say there is a dropoff, I need to explain this. It is actually a publication lag. A study that is going on that is involving this year may not come in publication for another couple of years, so there is a lag between the case occurs and when it gets published. But there is a trend here definitely showing that clinical failures are occurring in parallel to the resistance rate.

[Slide.]

So, regardless of the mechanism, we see resistance and treatment failures. Different studies have confirmed this, studies from the United States, Canada, Dr. Low and colleagues, as well as in Spain and Belgium. These treatment failures, as Dr. Bartlett points out, microbiologic data is very good, because it's from the blood, we know that it is a pneumococcus.

Unfortunately, as occurs in modern medicine now, we hardly ever get sputum. What this means you then have to realize is it is a tip of the iceberg effect. The bacteremias are less common but it is the part we see. The part we see is the failure with the bacteremias. But realize there are at least four patients who may have it in their sputum but is not being detected clinically. So this is really an underreporting of the treatment failures that have occurred and that trend line shows that the treatment failures continue to increase.

[Slide.]

The references for this is a review study, two publications that came out after review, recent data from the CDC published at a meeting two months ago. The resistance rates are from the CDC, two publications, as well as the CDC web site with the Active Bacterial Core Surveillance data on the slide.

MR. MOYER: You have now heard a little bit about the postmarketing surveillance regarding antibiotic resistance in both in vitro and clinically. I would like to switch now to our safety data by Dr. Barbara Rullo on the postmarketing information that we have available to us on telithromycin.

Dr. Rullo.

Clinical Safety

Barbara Rullo, M.D.

DR. RULLO: Members of the Committee, representatives of the FDA, good morning.

[Slide.]

I am Dr. Barbara Rullo from Sanofi-Aventis and I work in Global Pharmacovigilance &

Epidemiology. I welcome the opportunity to share with you this morning our safety experience with telithromycin since the drug was approved in April of 2004.

[Slide.]

First, I am going to briefly introduce you to the postmarketing safety team that has been working on telithromycin since actually the first year of PN approval. I am also going to describe for you our augmented pharmacovigilance initiatives that were implemented prior to U.S. approval.

We will also examine the overall safety of telithromycin postapproval and then, later on this afternoon, we will look at the specifically hepatic safety experience postapproval and then tomorrow we will look at the overall safety experience with regards to visual and syncopal events, as well as exacerbation of myasthenia gravis, and then conclusions.

I hope what you will hear is that telithromycin has been well studied and intensively investigated in order for us to understand the

risks associated with the product. As with all antibiotics, telithromycin is not without risk. But we understand what these risks are and have taken action to communicate them to health care professionals and patients in order that they be managed appropriately. Therefore, we believe telithromycin has a favorable benefit-risk profile.

[Slide.]

The postmarketing team that has studied the safety of telithromycin includes those within the company, as well as external thought leaders. Within the company we have the same group of physicians and epidemiologists with varied clinical expertise that have worked together as a team since January 2001, externally, thought leaders in hepatology, hepatopathology and cardiology, again the same group of physicians have worked with us to understand our postmarketing safety data since 2002, and for neurology and neuro-ophthalmology, also the same group of physicians have worked with us since 2003 in order to understand the safety profile of telithromycin.

[Slide.]

As you heard earlier this morning, the product was first approved in Europe in July 2001. This means we had a vast amount of postmarketing safety experience prior to U.S. approval.

Currently, there are an estimated 28 million exposures--that is, 28 million courses of treatment globally and about 6 million of these are in the United States.

[Slide.]

Now, since we are going to spend a great deal of time talking about out postmarketing experience, I think it is important to say a few words about spontaneous reports.

We all understand the strengths and weaknesses of spontaneous reports, however, they do remain the cornerstone of our safety surveillance for marketed products.

They help us to identify serious, rare events that are not detected during the clinical program. They enable us to better characterize uncommon events that are seen during the clinical

program and they provide additional safety information about subpopulations but there are important limitations.

Lack of essential information, limits of causality assessment. Lack of comparator information limits interpretation. Over-reporting and under-reporting limit accurate quantification.

Accumulated individual case reports do not equal an incidence rate. A reporting rate is not an incidence rate. A reporting rate is a measure of reporting intensity, and, as such, it is affected by many things.

It is affected by the severity of an adverse event. It is affected by time since launch. Higher reporting rates are reported shortly after a product is launched and as a physician becomes more familiar, gains experience with a product, their reporting rates decrease.

Stimulated reporting will affect reporting rates as you will see later today and tomorrow.

Secular trends will affect reporting rates as we will also see later today.

Finally, the health care professional inclination to report.

But with all of these caveats, nevertheless, spontaneous reports are an important and unique component of our safety assessment of marketed products.

Reporting rates are an important tool, they are a tool that we use for exploratory purposes in order to help us gain an understanding of the significance of an event and to decide whether or not further evaluation is needed.

[Slide.]

As you saw from our briefing document, and we will be discussing later today and tomorrow reporting rates, I want to emphasize how we determined our reporting rates.

Our reporting rates are expressed in number of cases per million prescriptions. We use this reporting rate calculation since telithromycin is used in an acute setting, it is used for an acute infection, short term, 5 to 10 days, and therefore we believe this is the more appropriate

reporting rate calculation to use.

[Slide.]

How did our overall postmarketing safety experience compare to the safety experience we saw during our clinical program?

Well, as you heard earlier today from Dr. Edelberg and Dr. Alexander, the most commonly reported adverse events during our clinical program were gastrointestinal: nausea, vomiting, diarrhea. We also saw dizziness, headache, some skin reactions, as well as malaise.

In the postmarketing setting, these were also among the most commonly reported adverse events. The only real difference between our clinical program and the postmarketing setting is that visual events accounted for an uncommon report in the clinical development program. But in the postmarketing setting, they accounted for about 25 percent of all the reports we received and we attribute this to the fact that because visual events are uncommonly associated with an antibiotic, that they were more likely to be

reported.

[Slide.]

How did our postmarketing safety experience in the U.S. compare with our postmarketing experience outside of the U.S.?

Well, from the first year PN approval, in July of '01 to December of 2003, there were 29 months with an exposure of about 6 million.

From the U.S. approval to September of this year, there were also 29 months with an exposure of about 6 million. So, if we compare the safety experience during these comparable periods of time, how did they compare if we look at the most frequently reported events using reporting rates as a measure?

You can see for nausea, vomiting, diarrhea, the reporting rates are very similar and also for blurred vision, visual disturbance. Where you do see a difference, as with accommodation disorder and diplopia, we feel that these differences are not real differences in the event that was actually occurring in the patient but

rather in the reported term.

[Slide.]

Again, for dizziness, headaches, skin reactions and malaise, you see very similar reporting rates.

[Slide.]

I want to next describe for you our augmented pharmacovigilance initiatives that were initiated prior to U.S. approval.

We wanted to make sure that we identified and evaluated our postmarketing safety reports as comprehensively as possible. Therefore, prior to U.S. approval, we implemented systematic data gathering activities. Beginning in May 2003, we used a questionnaire and this was used to standardize and maximize the data that we collected in order to ensure as comprehensive a review as possible of each spontaneous report of cardiac, hepatic and visual events.

In addition, with these events of interest, we had intensive follow-up of the adverse events. Typically, we would send at least two,

usually three, letters requesting follow-up information and, when indicated, we would have direct phone contact. This was especially true if an event was a new, unlabeled event or serious event.

Now, while we realized that these data gathering activities and follow-up activities do not ensure complete information, we did find that they enhanced the available data.

So what did we do with all this information that we were collecting? Well, prior to approval in the U.S., beginning in August of 2003, we began expediting all serious hepatic events.

This means whether the event was in the label or not, whether it was a U.S. case or a foreign case, we would expedite these reports; that is, we would send them to the Agency within 15 days for their review. This exceeds the normal regulatory requirements. We did this because of the emerging macrolide-like, hepatic effects of telithromycin.

[Slide.]

What else did we do with all these data that we were collecting?

We wanted to ensure that all available evidence was used in our decision-making processes, therefore, we implemented processes whereby we would comprehensively review all the data that we were gathering.

Prior to approval, we began to do routine cumulative reviews of each spontaneous report for cardiac, hepatic and visual events. We began doing that in January of 2002 and we continued to do it every six months to the present.

In addition, as a result of our second approvable letter, in January of 2003, as you heard earlier, we performed a cumulative review of all postmarketing reports so that we were doing the routine reviews. Now we also did a cumulative review of all of our postmarketing reports in January of 2003. Then monthly thereafter we continued to do cumulative reviews of all postmarketing reports. Then this culminated in

December of 2003 with one comprehensive report of all spontaneous reports and this is based on exposure of about 6 million patients outside of the United States.

[Slide.]

What did we do postapproval? Well, in addition to the routine cumulative reviews that we were doing, we did in-depth, qualitative, targeted reviews based on our safety surveillance.

As you heard from Dr. Edelberg, we also performed a postmarketing visual commitment study in order to better characterize the visual events and I will describe this in more detail tomorrow.

In order to evaluate potential mechanisms for the visual and the syncopal events, we did preclinical studies. In order to put the adverse events in context, we did comparative reporting rate analyses using FDA Freedom of Information extracted data.

Then, in order to assess comparative risk for hepatic events, we did two pharmacoepidemiologic studies, one, a retrospective

cohort study using PHARMetrics data-- you will hear more about this later on this afternoon from Dr. Wanju Dai--and the other, a retrospective cohort study using Ingenix research data. You will hear more about this later on from Dr. Alex Walker.

[Slide.]

When we did identify a risk, we ensured that it was communicated through as many channels as possible, through our sales reps and handouts and presentations, in mailings to our physicians, on the Ketek.com web site, in educational and CME programs and, in the case of myasthenia gravis, this was communicated to the myasthenia gravis organizations, as well.

Therefore, as we go through the next couple of days, and we describe for you our safety experience in the postmarketing setting with regard to the specific events of interest, I ask that you keep in mind these pharmacovigilance initiatives that we implemented, our data gathering activities, our intensive follow-up, our routine cumulative reviews, our comparative reporting rate analysis,