these data a little bit more deeply probably expanding the diagnostic categories, looking at people who had multiple doses.

It is probably the richest dataset we have to begin to address that question beyond the spontaneous reports. So I think there is a signal here around double dosing, whether it is two doses of telithromycin or whether it is telithromycin and a macrolide and what the sequence effects are. It is the kind of thing we are going to start looking at.

DR. HECKBERT: Yes. I think I took from that that multiple courses of the drug are being used more commonly than I might have expected. That is what these suggest.

DR. FAICH: I can't tell you whether that is an uncommon pattern or not except that we saw that kind of multiple dosing in the clari arm as well.

DR. LEGGETT: Could I make a comment?

DR. EDWARDS: Yes.

DR. LEGGETT: I am a specialist but I

would say it is almost the rule that people come to me--when they make it to me, they have had sequential doses, often it is in the same class. That is not unusual at all.

DR. MOYER: We do have information from the PHARMetrics database that Dr. Dai can provide specifically because that was looked at in her analysis. Dr. Walker saw the signal and has not further evaluated that yet within the database which needs to be done because, as you know, that was just recently completed. That is why we didn't make that presentation.

DR. DAI: I think there are two questions. One is regarding use in multiple antibiotics and the second one regarding duration. Let me address the first one regarding multiple antibiotics.

In our study, we did look into patients who may have taken more than one antibiotic regardless of which kind of combination in this 40-day window. Slide on, please.

[Slide.]

This is adjusted by the covariates listed

below. There are thousands of patients taking multiple drugs with telithromycin. There were also patients taking multiple drugs without telithromycin. You can see that, basically, the risk ratio, using Augmentin as the reference group, is higher than if you are taking only one antibiotic.

These are the adjusted number of prescriptions. We have another one which adjusts by duration of prescription as well as one of the covariates. It shows, actually, similar data.

Slide on, please.

[Slide.]

The difference between this one and the previous one is the same covariates are adjusted but this time we placed duration of any antibiotic use to the one used previously of number of prescriptions. You can see here this ratio is higher than single antibiotic use. Multiple antibiotic use with or without clarithromycin has increased risk but about the same magnitude.

DR. MORRIS: What was the time frame used

when you say multiple drugs?

DR. DAI: These are within the 40-day window, the risk window. We use a 40-day window.

DR. MORRIS: So it could be any combination.

DR. DAI: Any combination. In other words, multiple antibiotic use seems to indicate the underlying condition has severity of disease or some other cause of the underlying condition rather than because of antibiotics per se.

DR. EDWARDS: Thank you. Dr. Wong-Berenger?

DR. WONG-BERINGER: Related to that same question, on the multiple drugs, are they all antibiotics or other drugs as well?

DR. DAI: No. We are only talking about antibiotics.

DR. WONG-BERINGER: I guess this is a question where it relates to duration of exposure or the magnitude of drug exposure. Was there a pattern of concomitant medications other than antibiotics or including antibiotics that have been

identified in the patients who develop disturbances in consciousness or in visual disturbance.

DR. MOYER: Your question is visual disturbances and loss of consciousness--could you repeat the question?

DR. WONG-BERINGER: My question is has there been a pattern identified with concomitant medications that perhaps, through altered metabolism, increase the exposure of Ketek and, therefore, may be related to the disturbances seen.

DR. MOYER: Disturbances in visual or loss of consciousness. This would be combination therapy that might alter that. Dr. Rullo, do we have that information?

DR. RULLO: We did look at this originally at the time that we had done the integrated overview of visual events and we couldn't find any pattern in terms of concomitant medication and visual events because of females, we were looking for things like hormonal therapy or hormone-replacement therapy, birth-control pills.

We were also looking for antihistamines.

We thought, because they can have an effect on blurred vision, and we couldn't find any pattern at all.

DR. KOSKI: If I could augment on that, if you would stay up there for just a second. I notice one of the complicating diseases that you noted for syncope was myasthenia gravis. This is not a common issue with these patients although some of them that are on anticholinesterase inhibitors such as peritostigmine can develop bradycardia if they are very sensitive.

I sort of wondered, number one, what was the frequency of myasthenia gravis patients that had syncope and, two, whether the peritostigmine treatment might not have been a complicating factor.

DR. RULLO: I would have to get back to you on that. I don't know the exact information. Thank you.

DR. JOHANN-LIANG: Can I just follow up with--regarding people with visual events, remember we had said that a lot of them were young females

and not necessarily--they don't take other drugs. These are healthy populations having visual events so we didn't see anything with concomitant meds.

Regarding issues with loss of consciousness, we are worried about drug interaction in the subpopulation that may have cardiac. Remember, it is labeled for its drug interaction, ketoconozole-like issues. So that is a very good point.

DR. ALEXANDER: Remember one of the presentations I made yesterday, with regard to the visual and the controlled clinical trials. was in the controlled clinical trials for visual effects there was a signal if we looked at those patients who were receiving the concomitant CYP 3A4 inhibitor where there was a slight increase in terms of the proportion of those patients who were receiving the visual symptoms. But you are still talking about what is a relatively small number of patients.

So making conclusions about what the potential for the concomitant use of those kind of

medications were contributing to these more severe events, it is hard to tell.

DR. EDWARDS: Dr. Marco.

MR. MARCO: This is more of a comment than a question. I just have to say that we have known for some time these adverse events, whether it be the visual disorders, the loss of consciousness or the exacerbation of myasthenia gravis. It just seems that putting wording in, no matter how carefully it is written in the Patient Package Insert is just not sufficient.

Patients don't read the inserts. They don't. I think that is just a huge problem but I don't know how to fix that. Even though you have been in contact with the Myasthenia Gravis Foundation and probably had some type of article in a newsletter, it is a great thing.

But with all these side effects and how severe they can be, it doesn't seem like it has really been a strong effort to really get the word out to protect patients.

DR. EDWARDS: Thank you. Are there any

other questions or comments at this time? We have gotten ahead of schedule. What I would like to do is take a break at this point until 10:15. We will be then resuming a bit ahead of schedule. I think we are going to need that time as the morning goes on. Thank you.

[Break.]

DR. EDWARDS: Before we turn the meeting back to the sponsor, I would like to ask Dr. Soreth--I believe you had a comment about some remaining points from the last discussion regarding the ophthalmology.

DR. SORETH: Thank you, Dr. Edwards. I wanted to ask Dr. Wiley Chambers, our Deputy Director in the Division and an ophthalmologist, if he would make some comments with regard to his review and his perspective of the review of the visual adverse-event cases with telithromycin as he has also reviewed them.

DR. CHAMBERS: I am Wiley Chambers. I am the Deputy Director for the Division of Anti-Infective and Ophthalmology Products. I would

like to take just a couple of minutes to put in perspective some of the ocular events and ask everybody to think back.

Let me start off with thinking back to the last time you were sick and think whether your vision was perfect at that particular point in time. If you now enhance the fact that we believe Ketek does have an effect on the visual system, at least in some portion of the patients, an so you are magnifying people, asking people, whether they have had effect on their eyes, you are likely to get more reporting and everything comes up as far as numbers.

We unfortunately have a wide variety of ways that people describe how well they see. Those people that have glasses, if you take your glasses off, are you blind? Many people will describe it to somebody else as, oh, I am blind, I can't see, when their vision is blurred.

To an ophthalmologist, there is a very big difference between blindness and having your vision blurred. But, on case-report forms, we don't have

the options to go and talk and ask those particular questions of people.

From our review and from the studies that were done, we have not seen anything in the retina or in the neural system. That doesn't mean that there isn't definitively nothing there but we have not, with our sophisticated tests, been able to find it.

That doesn't mean that some day somebody won't develop a better test and we may be able to detect what they are, but we are not there yet. These are our common diagnostic tests.

That coupled with we were able to magnify the dose--in other words, you heard there were people given 2400 milligrams and we were able to change the percentage of people with visual effects from this 1 to 2 percent up to about 20 percent. That was, then, enough to be able to study. So we were then able to do measurements on accommodation as well as measurements on a whole wide variety of different things.

We looked at visual field, visual acuity,

a wide variety of different events. The only thing we were able to come up with was the accommodation. Now, that said, do I believe that accommodation accounts for all of the events? No. But it probably accounts for 90 percent of the events.

So, if you take that 90 percent of the events now off the table because it is accommodation, yes, we have a background of a few other events that are comparable to other products. Those are a wide variety of different things. They are not necessarily related to accommodation.

I don't begin to say that every event that we see is due to accommodation. But that doesn't mean the vast majority of them are not due to accommodation. I think there needs to be that separation.

Thank you.

DR. EDWARDS: Thank you very much. We will now return to the sponsor. Dr. Mark Moyer will introduce the next three speakers.

DR. MOYER: There was a question before regarding myasthenia gravis and how many patients

had syncope. There were two. Thank you. So we did want to address that question. We will have the risk-management plan that will be presented regarding myasthenia gravis, what has been done and what is planned to be done to continue that effort in one of our presentations that is coming forward.

Sponsor Presentation

Treatment Options for Respiratory Tract Infections, Role of Telithromycin

DR. MOYER: I would now like to switch our attention to the efficacy of telithromycin and how that relates in the role of respiratory-tract infections. We have an overview and also a presentation on community-acquired pneumonia by Dr. Daniel Musher. He is a professor of Medicine at Baylor College of Medicine. He will provide his perspective on the treatment with telithromycin.

Overview and CAP

DR. MUSHER: Good morning.

[Slide.]

I will make some comments on pneumonia, the causative organisms and the possible role of

various antibiotics in treating this infection.

[Slide.]

I do have funding through the V.A. Merit Review Program. I have got active grants to study C. difficile which is an area I have begun to study the last couple of years. I had a grant from industry maybe in 1998-2001. I don't participate in speakers bureaus. I have got no ongoing consulting arrangements and my fee for this conference is going to go directly to charity.

[Slide.]

A reductionist might view the respiratory tract as a single tube without pouchings. There is the middle ear, sinuses, bronchi, alveoli. The upper part of this complex system is regularly colonized by certain bacteria, pneumococci, Hemophilus, Moraxella, Staph aureus, other organisms that tend to cause infection when they are acquired, some of the viruses, Chlamydia, Mycoplasma and Legionella.

When treatable organisms are present, antimicrobial therapy is indicated. The problem is

that the clinician often doesn't know and is left with decision to treat based on clinical findings.

I guess I ought to have mentioned--I'm sorry, just about myself. I do round on the clinical infectious-disease consulting service three months a year and I round on general medicine three months a year, so I really do have a very heavy ongoing commitment to clinical medicine as well as to my research which has largely dealt with Hemophilus, pneumococcus, Moraxella and Staph aureus.

[Slide.]

I thought you might be interested in this. This is the causes of pneumonia in the pre-antibiotic era. It is taken from Heffron's book, 1939. You can see the pneumococcus was the overwhelming cause. This Streptococcus is Strep pyogenes. Friedlandler's bacillus was Klebsiella. The influenza bacillus, for your interest, that was H. flu. Actually, when I began working on H. flu and I showed that it is a fairly common cause of the pneumonia, this is what the state of the art

was. It was thought to be a very uncommon cause of pneumonia, just for your interest.

[Slide.]

At the present time, the data are much more difficult to determine. There is less emphasis, as John Bartlett pointed out yesterday, in microbiologic diagnosis. There is a lot more emphasis on prompt administration of antibiotics.

I remember, in the late 1960s, when the chapter Textbook of Medicine was written by Dr. Austrian and there was only a single chapter on pneumonia and it was also the chapter on pneumococcus.

I went up to Dr. Austrian. I said, "Dr. Austrian, do you really think all of those pneumonias are caused by pneumococcus?" He just about patted me on the head and said, "Young man, they certainly are."

Well, we do think that many or most of them are. It is very difficult to determine. In the Years 2000 to 2005, even when a specimen was submitted, pneumonia was not detected by routine

lab in more than 50 percent of cases of proven bacteremic pneumococcal pneumonia. I published that in Clinical Infectious Diseases last year.

The Infectious Disease Society, IDSA, and the American Thoracic Society, ATS, Guidelines both do agree that Streptococcus pneumoniae is the most common cause of pneumonia leading to hospitalization.

I do want to talk for a few minutes--I would like to summarize the information on pneumococcus as I understand it relating to the susceptibility of pneumococcus to various antibiotics.

[Slide.]

So, in the 1990s, the most prevalent types in children, 4, 6B and so on, these were also the most likely to be antibiotic-resistant. That is, of course, because the little kids are colonized. They are passing these things around to each other, often at day-care centers and at schools. That is where most of the antibiotic pressure is. So it will be no surprise that there is high level of

antibiotic resistance in the most prevalent organisms.

Now, those are the pediatric strains. But, of course, we adults--I'm staying with my daughter. We have got three little grandchildren. Needless to say, I am picking up pneumococci these next few days and these are probably the ones I am picking up.

When the protein-conjugate pneumococcal vaccine was introduced--I will call it Prevnar because it is jus easier to say it. When that was introduced in 2000, the widespread use led to a spectacular decrease, a stunning decrease, in pediatric infections by these types of pneumococcus. It was really remarkable.

However, to make it very clear, what has happened is there have been replacement strains of pneumococci. These are new strains that are not included in Prevnar. For example, Type 6 which is non-B, Type 19 which is non-F, Type 35, 11 and 15. These things have come and they have replaced the ecological niche that was lost when some of these

other--when we, as a result of the conjugate vaccine, developed antibody to these originally prevalent pneumococci.

[Slide.]

The replacement strains originally were presumably susceptible to antibiotics. However, they have been subjected to the same antibiotic pressure in day-care centers, et cetera, and they also show increasing antibiotic resistance.

Thus, the overall rate of antibiotic resistance among pneumococci fell in the first few years of Prevnar but it is back up. It has increased and is now back to the 2001 level.

In 2005, pediatric isolates showed a resistance to amoxicillin of 5 to 10 percent, erythromycin and other macrolides 30 percent, and trimethaprim sulfa which I will also call Bactrim because it is just easier, 40 percent.

The replacement strains are not targeted by the 9-valent or the 11-valent vaccines that are now under development.

[Slide.]

Here is some data that was just presented at the Infectious Disease Society Meetings a few months ago from the Protekt study which we heard about from Dr. Jenkins. Isolates from adults tend to be more susceptible than those from kids. There is not much level in adults, not much difference in the levels of antibiotic resistance in 2003 versus 2005. About 6 percent of adult isolates are resistance to amoxicillin, 25 to 30 percent to macrolides and Bactrim, 1 percent to quinolones, close to 0 percent to telithromycin.

[Slide.]

Let me now deal with the recommendations for treating pneumonia. In 2000 and again in 2003, the Committee for the Infectious Disease Society, of which Dr. Bartlett and I are members, recommended in no particular order, azithromycin, doxycycline, amoxicillin or amoxicillin/clavulanic acid which, again, I hope you don't mine, I will call Augmentin because it is easier, or a respiratory quinolone.

In 2006, as a result of the IDSA and the

ITS getting together, there is a Joint Guideline Committee. So, in one of these games of elimination, John Bartlett and I remained on the committee. We are two of the five IDSA representatives and there are five ATS representatives. Dr. Sethi is one of those.

So, to the original version, we added telithromycin if there are no risks for enteric gram-negative organisms. In other words, clarithromycin was viewed as being extremely effective against respiratory pathogens unless there is some reason to think that there is going to be a gram-negative bacillary pneumonia which is a small but important subpopulation among all those adults who might get pneumonia.

[Slide.]

Now, the IDSA, in 2006--IDSA and ATS had joint guidelines. This is what these guidelines now state. They have been rewritten because of the deliberations of this committee.

They state that telithromycin is active against S. pneumoniae, resistant to other

antimicrobials commonly used for community-acquired pneumonia, penicillins, macrolides and fluoroquinolones. Several community-acquired pneumonia trials suggest that telithromycin is equivalent to comparators and they added telithromycin for the treatment of community-acquired pneumonia, Level 1.

Level 1, as you know, is the one that is regarded as the best supported by evidence if there are no risks for enteric gram-negative rods.

[Slide.]

In regions with more than 25 percent high-level macrolide-resistant pneumococci, consider the use of alternative agents--that means alternative to the original list which really means telithromycin.

I will remind you that, in that map that you saw yesterday, the western part of the country, the macrolide-resistance rate is 21, 22 percent. In the middle of the country, in the eastern part of the country, it is already well above 25 percent.

So, again, that speaks to the need for another antibiotic other than the macrolides. There have been reports--this is the way the IDSA, ATS, document is now in press. I think for the purpose of this committee it is important that I state this so I don't think that I am violating any confidence by doing this. "There have been reports of severe liver toxicity and the reader should refer to any new information regarding appropriate prescribing of the agent."

The final point; "At present, the Committee," meaning us, the recommending committee, "is awaiting further evaluation by the FDA of the safety of this drug before final recommendations." So there is a very heavy weight of authority on this committee.

But, as far as the view of the IDSA and ATS--oh, and I didn't mention, John Lonks is a member of that committee. There are a number of us who are active in that committee. As far as the view of the committee is concerned, telithromycin is a highly effective and an important

antimicrobial agent.

[Slide.]

Let me address very briefly this macrolide-resistance. Is it clinically significant? Just very briefly. There have been small case series of patients failing treatment with azithromycin. First, there were case reports just as John Lonks pointed out. Then there were small case series.

I happen to report someone who, on treatment with azithromycin, the organism mutated and became resistant and this young person died. There have been fairly large case-control series in which patients with pneumococcal disease who were taking a macrolide at admission are shown to be infected with macrolide-resistant isolates a lot more commonly than you would expect from the rate of macrolide resistance of the population and there are a number of studies like that including a very recent one from the CDC at the ICAAC meetings in the fall of 2006.

How would telithromycin do in these cases?

Based on data obtained in Phase III studies, telithromycin seemed quite effective. It cured 67 of 76 patients with bacteremic pneumococcal pneumonia including 8 of 10 caused by macrolide-resistant pneumococci.

[Slide.]

Let me address quinolone resistance, very briefly. I don't know how many of you realize I write the pneumococcus section for Harrison's, the pneumococcus and the Moraxella. But the young people don't read Harrison's anymore. They have this electronic UpToDate. That is all anybody reads. They certainly don't read--I write the pneumococcal chapter for Mandell's, this long scholarly chapter. Forget it. UpToDate. UpToDate is what they read so they asked me to write that one.

The first time they asked me, I turned them down. I had never heard of an electronic textbook. That is another story. Quinolones are recommended as treatment options and they are widely used in respiratory infections. Very

effective drugs for such purposes.

The overall level of pneumococcal resistance to quinolones in the United States is 1 or 2 percent. Tiny. Many isolates that are called susceptible already exhibit the first of a series of mutations. The effect of mutations is likely to be additive. It is believed that a second mutation will lead to resistance. The infectious-disease community tends to believe that we are on the threshold of the emergence of a substantial rate of quinolone resistance.

Resistance in the community is certainly associated with increased use of quinolones. This was shown by Dr. Low and others in the Canadian experience and reported in The New England Journal of Medicine.

There are pockets of increased resistance. For example, nursing homes where levels approach 15 percent. They have gone to nursing homes and they have done nasal swabs and they found, when they isolate pneumococci, 15 percent of them are resistant to quinolones. That is because there are

lots of quinolone use in nursing homes. The drug can be given orally. They are "broad spectrum." They are widely used.

[Slide.]

Historically, such pockets of resistance heralds spread to the community at large. There are also case reports of clinical failures associated with infection by quinolone-resistant strains, and there are several of these.

Now, there are three important additional points. Actually, I don't think the first one is so important. I thought there was anticipated use of quinolones in little children. I am not sure what the status of that is but, when I lecture to the residents, the medical students, I say that as soon as a quinolone appears for pediatric use, it effectiveness against pneumococci is going to be gone very, very rapidly.

I don't know what the state of that is. I thought that it is still being discussed to develop one. I am not sure.

There are, and these next two points I am

very certain about, societal concerns over the widespread use of quinolones and the resistance of gram-negative rods. The quinolones are what we clinicians like to use to treat urinary-tract infections because of the high rate of resistance of E. coli to drugs such as Bactrim.

As you heard yesterday, the rate of E. coli resistance in the community is now at about 10 percent and rising. So that is of some concern. The more widely the quinolones are used for respiratory infections, the greater the increase will be in the resistance among these organisms that cause urinary-tract infections.

C. difficile, which, as you saw from the second slide, is one of my current special interests. C. difficile infections are increasing not just in hospital but also in the community. They are very highly quinolone-associated. C. difficile infection is a very nasty disease. That is of a concern as a result of quinolone use.

[Slide.]

So, in summary, telithromycin is broadly

effective against respiratory pathogens include the so-called typical and the so-called atypical causes of community-acquired pneumonia with a negligible rate of documented resistance of pneumococci to date. Telithromycin has minimal activity against anaerobic flora and none against enteric bacilli. That limits its undesired antibacterial effects.

The overall safety of telithromycin--this was, to my view and, as I say, the committee is going to deliberate and the committee is going to decide--to my view, the overall safety of telithromycin does not appear to be very different from that of other drugs that are used to treat the same respiratory infections.

[Slide.]

The resistance of pneumococci to macrolides, tetracyclines and Bactrim is widespread and clinically significant. Resistance of pneumococci to quinolones is low but it is increasing in proportion to use and there are additional problems with quinolone use including impending pediatric use, increased resistance of

enteric bacilli and the predisposition to C. difficile.

Finally, to my knowledge, there are no other effective oral antibiotics "in the pipeline." That means in development. So this is a very important antibiotic. We don't have a lot of new ones coming along.

[Slide.]

In conclusion, telithromycin appears to me to be an important option for treating outpatients who have upper and/or lower respiratory infections including acute bacterial rhinosinusitis, acute exacerbations of chronic lung disease and community-acquired pneumonia.

Thanks very much.

DR. MOYER: Thank you, Dr. Musher. Our next presentation will be by Dr. Sanjay Sethi. He is associate professor at State University of New York at Buffalo. He will be presenting on the acute exacerbations of chronic bronchitis, the etiologies, outcomes and antibiotics.

AECB--Etiology, Outcomes and Antibiotics

DR. SETHI: I would like to thank the committee for this opportunity to present information from my perspective about acute exacerbations of chronic bronchitis.

[Slide.]

I am a pulmonologist, I guess about the only one interesting room, maybe. But I actually defected over to I.D. to do my research and have actually worked--Dr. Bartlett did a nice job of summarizing some of our work over the last 15 years which has focused on the role of bacteria in exacerbations.

[Slide.]

I would like point out that we have used different tools to look for whether bacteria cause exacerbations. At this point, it is generally agreed that about 50 percent of exacerbations of chronic bronchitis and COPD record related to bacterial infection.

I would like to point out that Dr. Bartlett focused on the Hemophilus, but, in terms of the acquisition of strains of bacteria and

development of specific immune responses, we have been able to also demonstrate that, for the pneumococcus and Moraxella catarrhalis so we have good evidence from those lines of evidence that those three bacteria are important in causing exacerbation of chronic bronchitis.

[Slide.]

There has been a lot of discussion about outcome of exacerbations. Since yesterday, I heard several times, oh, these are mundane illnesses which are self-resolving. Well, let's look at the data. I have summarized several studies, a lot of them very well done and in very good journals, which have examined the outcome of exacerbations in the inpatient setting and the outpatient setting.

In ICU patients in-hospital mortality has ranged from 11 to 24 percent. In hospitalized patients, hospital mortality has ranged from 6 to 8 percent. That is comparable to community-acquired pneumonia.

In outpatients--people always ask me what is the mortality in outpatients. I tell them

mortality is not a good measure. We are not doing our job right if we have mortality with exacerbations in outpatients. We need to be looking at morbidity. The way to look at morbidity is by looking at relapse rates and treatment-failure rates.

So, again, in E.R. patients, the relapse rates have been 19 to 32 percent. In outpatients, in office settings, the treatment-failure rates in observational studies have ranged from 13 to 32 percent.

Furthermore, up to about, depending on the study, 16 to 52 percent office-treatment failures get hospitalized with all the adverse consequences and costs associated with hospitalization. So exacerbations are not benign, based on at least all these studies and all the information that has been gathered over the last ten years.

[Slide.]

The other concept of spontaneous resolution of exacerbations I heard a lot about since yesterday, and I would like to give you my

perspective from studies that are out there.

There is still only one really good placebo-controlled antibiotic trial in this field. There are others which have got several limitations. This study from Nick Anthonisen also has limitations. But let's look at the study.

In this study, in the yellow bar, overall, is shown the spontaneous resolution at three weeks in these patients. That is 55 percent. So yes, there is a proportion of spontaneous resolution but 45 percent of patients have not resolved over three weeks.

Again, let me point out, over these three weeks, these patients are not just sitting around with a slight cough and sputum. These are patients who are dyspneic. These are patients who can't even do their normal activities of daily living, the independent activities of daily living.

They have fatigue. They have sleep disturbances. These are all well-documented consequences of exacerbations. So the time of resolution is long in these patients and is

incomplete in many situations.

Now, we heard data from Dr. Bartlett about Type 1, Type 2 and Type 3. As you can see, the benefits with antibiotics seems to be in the Type 1 and Type 2 exacerbations which means at least two of the three cardinal symptoms are present.

So, based on this, do we need placebo-controlled trials? Well, we do need placebo-controlled trials but, in these kinds of patients, in relatively mild exacerbations. That is one question where we need to ask questions, can placebo-controlled trials tell us better about who to treat and who not to treat with antibiotics and whether they have any benefit.

If we do placebo-controlled trials in these more severe patients, then we need a lot of safety provisions over there so that we don't do harm to patients. But, more important than that, I think we need to have better outcomes.

If we show tomorrow in a placebo-controlled trial that, at 3 weeks, the patient is about the same as with an antibiotic,

that doesn't have much clinical significance. These patients are acutely sick. What they are more interested in is how fast they get better. So we need to have better outcomes. I know there are PROs in development to address those outcomes and exacerbations.

[Slide.]

What happens to the patients who don't improve. Well, a certain proportion deteriorate, again from the Anthonisen study, in all patients. 18 percent of the patients deteriorated and, of course, that deterioration results in additional visits, results in hospitalizations, et cetera, versus 9 percent in the antibiotic group.

Again, the benefits seem to be with Type 1 and Type 2 exacerbations. You will be hearing later from somebody from Sanofi but I have looked at those AECB studies and a large proportion--there are some patients who may be in this group over here. But a large proportion of the patients belong to this kind of grouping. So one can really say that there are patients in whom there is

benefit demonstrated with antibiotics out there.

[Slide.]

Well, that is the one study. How about systematic analyses? You saw one systematic analysis yesterday. I will show you the latest one. Again, with the caveat. This applies mainly to moderate to severe exacerbations. It doesn't apply to mild, really mild, exacerbations.

If you look at the systematic analysis on the left side of the antibiotic-related studies--this is from the Cochrane database analysis which I think they do these things quite well. Essentially, you see that antibiotics reduce mortality by 77 percent. The numbers needed to treat are 1 in 8.

The decreased treatment failures and the numbers needed to treat is 1 in 3 to get that benefit. The major adverse effect reported in these studies was diarrhea. That happens in 1 in 7 patients.

There have been submissions out there but maybe all you need to do is dampen the inflammatory

response and use systemic steroids. So let's compare systemic steroids in the same Cochrane database analysis. The studies have not been able to show a benefit in mortality. You need to treat nine patients to prevent one treatment failure. You treat six patients. One in six patients get hypoglycemia.

So, in terms of benefit, more evidence is required. I would love to see more evidence and I have been involved in developing more trials and placebo-controlled trials for this. But I think there is enough evidence out there to tell us that, in moderate to severe situations, antibiotics work.

[Slide.]

In the next couple of slides, I will present you the pulmonologist point of view of the situation. This is the Gold Guidelines. These Gold Guidelines are a global initiative on obstructive lung disease. This is an initiative which is sponsored by pretty much almost every organization that you would know of, NIH, CDC, WHO, ATS, ERS, et cetera.

These Gold Guidelines are the latest version. It is available on the Internet. We recognize that patients not requiring hospitalization--that is what they call "mild,"--there is Hemophilus influenza, pneumococcus, Moraxella and possibly Chlamydia pneumoniae has a role in the exacerbations.

[Slide.]

These are the antibiotics that are recommended which include, of course, the narrow-spectrum agents but also include broader-spectrum agents including ketolides like telithromycin. One can say, oh, you have got all these drugs. Why do you need something like telithromycin. Well, because these patients get drug-resistant Strep pneumo.

I know there is not as much evidence out there as in CAP, but I would share with you one piece of evidence which may--these are in two slides that I added.

[Slide.]

This is from a cohort study which we have

been following over the years. What we asked in those patients was that if they had been exposed to a macrolide, what is the incidence over the next three months--if they have a Pneumococcus, what is the incidence of that being a macrolide-resistant Streptococcus pneumoniae.

What we found was that, if the patient had an exposure to a macrolide in the past three months, it was about 58 percent of those strains were resistant to a macrolide whereas, if they were not exposed to a macrolide, it was closer to the baseline rate of 18 percent.

We found similar phenomena for penicillin strains. These are both the nonsusceptible and resistant strains. Over here, we also found a similar trend. This did not reach statistical significance because of the smaller number of strains in that category.

[Slide.]

So, when they have these strains, when they have been exposed to macrolides--you know, the other thing to remember is that exacerbations are

recurrent phenomena. In moderate to severe COPD, exacerbations average at about two per year. In our cohort, antibiotic use is about an average of three times a year. But that is an average. There are numbers above and below.

So many times, these patients require repeated courses of antibiotics. In the current situation, I go to the quinolones. Thinking about all that we were discussing since yesterday, every antibiotic has got risk and benefit. The use of quinolones brought to my mind the fact that, in the last two years, I have had to hospitalize two patients, one with hypoglycemia and one with C. dif following treatment for exacerbations

So antibiotics have risks. Antibiotics have benefits. I think telithromycin, in my mind and, at least this point, in the mind of the Gold Guidelines, is a reasonable alternative for the treatment of exacerbations.

Thank you.

DR. MOYER: Thank you, Dr. Sethi. Our next presentation on the individual indications is

on antibacterials in acute bacterial sinusitis presented by Dr. B.J. Ferguson. She is an associate professor at the University of Pittsburgh School of Medicine.

Dr. Ferguson.

Antibacterials in ABS

DR. FERGUSON: Good morning.

[Slide.]

I am B.J. Ferguson. For the last almost fifteen years at the University of Pittsburgh I have been seeing and treating primarily patients with sino-nasal problems. I have done clinical trials in sinusitis for several pharmaceutical companies include Sanofi-Aventis. Just this past September, I presented before an advisory committee to the FDA on the efficacy data of gemifloxacin for Oscient Pharmaceuticals.

But, primarily, I am dedicated and devoted to trying to understand this disease and to provide the best possible care for my patients with sinusitis.

[Slide.]

The problem is that it is really difficult to differentiate between viral and bacterial disease on clinical grounds. So we reserve the diagnosis of acute bacterial sinusitis for patients who have been symptomatic without improvement for at least seven days or a worsening, a double sickening, who have symptoms such as purulent nasal drainage, nasal blockage, facial pain and pressure, or for those with fulminant symptoms, fever, unilateral pain, pressure, yellow drainage regardless of duration.

All guidelines would recommend an antibiotic for these patients and most would recommend a narrow-spectrum antibiotic.

[Slide.]

After otitis media, sinusitis is the most common indication in the United States for antibiotic prescription. In Piccirillo's review of sinusitis in the 2004 New England Journal, he cited a reference of a database of almost 30,000 prescriptions for the indication of acute bacterial sinusitis. In that database, two patients had a

complication; one, a brain abscess, the other meningitis.

So what we can say is that, in patients treated with an antibiotic for presumed bacterial sinusitis, the incidence of complications is rare, about 1 in 15,000.

[Slide.]

Because of the difficulty in differentiating between viral illness and bacterial illness, when we are doing trials for acute bacterial sinusitis we require higher standards. We require positive radiographs. We require trials that include maxillary sinus tap so that we can have bacteriologic data.

Until recently, it was considered unethical not to treat a patient who you truly thought had the disease with an antibiotic. So we performed noninferiority comparison trials.

[Slide.]

However, in 2003, an advisory committee to the FDA presented some of the data that will be presented to you today which I would like to

interpret for you. It came to the conclusion that, because placebo and antibiotics are so frequently equivalent in treating this disease, we need placebo-controlled trials.

They also recommended that different endpoints be used such as speed to resolution of symptoms and quality-of-life measures. In fact, in September and again in October of this year, two antibiotics were not approved because they did not do superiority or placebo-controlled trials.

[Slide.]

Now, what was the data that was presented to the advisory committees when they made these recommendations that placebo in antibiotics is equivalent for acute bacterial sinusitis.

This is a reinterpretation of a slide that you will see from Dr. Johann-Liang that was presented at the September meeting. What this shows is the studies in the literature that compare placebo to an antibiotic for the indication of sinusitis. You look at it and you say, my goodness; most of these are equivalent.

But if you study these cases, you will find that they do not have the rigor that we require in studies that we do for sinusitis for FDA approval. In fact, since the year 2000, only one of these studies had radiographs as an entry criteria and, in that study, only 40 percent, when they look back at it, had positive radiographs. In that particular case, the Buccor[?] study, one of the patients who was randomized to placebo had a brain abscess.

Nevertheless, in the conclusion of the abstract of that study, amox/clav and placebo are equivalent in treating sinusitis and amox/clav causes more diarrhea.

There is another study that I would like to highlight here and this is the Lindbaek study in 1998. It is included here even though Lindbaek, in his study, only enrolled patients who had C.T. evidence of mucosal thickening of greater than 1 centimeter. He excluded all air-fluid levels. He excluded all patients with opacification. He concluded that, in this population, a C.T. scan

with just mucosal thickening does not differentiate between patients who need an antibiotic and don't because placebo and antibiotic were equivalent.

Now, Lindbaek did a much better study for showing that antibiotics work. I am going to review that study with you in just a minute.

[Slide.]

Finally, these are the studies that were reviewed in the HCPR in 1999 that do use more rigorous criteria. In fact, when a systematic review of the studies by Cochrane in 2005 in HCPR and 2003 when they really looked at entry criteria, both agencies concluded that antibiotics were superior to placebo in treating this disease although there is a high spontaneous resolution rate of about two-thirds.

If you look at these studies which are actually a little bit better you will see the--Axelsson, you can't count because he irrigated all the sinuses. We know that sinus irrigation is therapeutic. Gananca and Lindbaek are our two best studies. Ellen Wald did her study in children.

Van Buchem--this is a study where he required radiographic criteria without duration of symptoms and the radiographic criteria included mucosal thickening of 5 millimeters or greater. Look. It crosses the line. Stalman had no objective criteria. These were patients who had symptoms for five days or greater. This was enriched for colds and antibiotics do not treat a cold.

[Slide.]

So let's look at one of the best studies we have. There are only two that are in the literature. This is Lindbaek's study in 1996 in which he randomized patients to one of two antibiotics plus placebo.

[Slide.]

What is nice about this study is he gave the patients a little daily diary. He asked them to talk about their symptoms but he also asked them to answer the question; do you think you still have sinusitis today.

If you look at the results of that, you can see that the patients who were randomized to an

antibiotic, at Day 10 of their antibiotic, 14 percent of them still thought they had sinusitis. But look at the patients who were on placebo. 43 percent of them still thought they had sinusitis.

If you follow this on out, you see that, even though this disease resolves spontaneously, at 30 days, the ones who were randomized to placebo, a third of them still thought they were sick compared to 10 percent of the patients who received an antibiotic.

[Slide.]

So I do think we need better studies with appropriate outcomes. I want to be clear about that, but I do think, in the kind of trials that we do, antibiotics are superior to placebo.

[Slide.]

Finally, in conclusion, what does this mean for telithromycin? Well, it has an attractive efficacy profile. It is narrow-spectrum. It has in vitro activity against resistant pneumococcus. I think is has done well-controlled studies

according to rigid entry criteria that meet and actually exceed a minus 10 percent noninferiority margin compared against good antibiotics like cefuroxime and Augmentin with TAP data.

But, ultimately, for me, in treating disease that so often resolves spontaneously, it is about risk. The risk of this antibiotic must be similar to other antibiotics that I would use in treating this disease.

So, with regard to the visual problems, for the last two years, I have been telling patients, you know, you can have visual problems with this antibiotic and it usually comes on quite rapidly. Don't take this antibiotic until after you get home. I don't want you driving right after you take this antibiotic.

With regard to myasthenia gravis, I am not going to prescribe this drug in myasthenia gravis. Hepatic toxicity is more worrisome. In fact, after the news about hepatic toxicity came out, I only used telithromycin one time, in a patient with a resistant pneumococci.

But the information that was provided yesterday, particularly by Dr. Lee, was very helpful to me. First of all, he showed me what kind of hepatic toxicity these patients usually have. Then he gave me an estimate of how frequently this occurs. He just said this at the end. He said that he thought that about 1 in 30,000 prescriptions was associated with hospitalization and about 1 in 200,000 was associated with acute liver failure.

These numbers are important to me because they are consistent with the same crude risk estimate that Dr. Dai presented from her PHARMetics database. In that PHARMetrics database, she showed that moxifloxacin has accrued risk of 8 per 100,000. Moxifloxacin is one of the antibiotics that we do use in acute bacterial sinusitis.

So, for me, until new information or new interpretations are provided, I do believe that the risk-benefit of telithromycin favors its continuation and availability for the treatment of acute bacterial sinusitis.

Thank you.

DR. MOYER: Thank you, Dr. Ferguson.

We have a brief final summary presentation by Dr. Bruno Leroy from Sanofi-Aventis. He is the Head of Internal Medicine within our Global Medical Affairs Department.

Dr. Leroy.

Summary and Conclusions

DR. LEROY: Good morning.

[Slide.]

I am Dr. Bruno Leroy. I am in charge of internal medicine, Global Medical Affairs, at Sanofi-Aventis. I would like to summarize the main points that we have made in the past two days or that we have summarized in our briefing document. I would also address some key elements of the risk-management activities.

[Slide.]

You have heard that respiratory-tract infections are very frequent diseases with an annual incidence ranging from approximately 5 million in community-acquired pneumonia,

9 million per year in acute exacerbation of chronic bronchitis to 20 million per year in acute bacterial sinusitis. It can be associated with morbidity and, in some cases, mortality. Mortality in community acquired pneumonia is around 1 percent in the outpatients but can go to up to 10 percent when they are hospitalized. In acute exacerbation, it was well described by Dr. Sethi recently.

In acute bacterial sinusitis, complications are rare but, as mentioned by Dr. Ferguson, they can be very serious.

Treatment of those infections is empirical in the majority of the cases. Ideally, antibiotics used to treat these diseases should have a spectrum of activity that focuses on the respiratory pathogens including also resistant strains.

Several respiratory-tract pathogens are now resistant to several antibiotics in vitro, in particular the Pneumococcus which is the most frequent and the most invasive of those pathogens. Physicians treating those infections need drugs that are active against those pathogens.

[Slide.]

Several classes of drugs commonly are used to treat respiratory-tract infections have now limitations, either because they have become less active, less effective to treat those pathogens because of resistance, mainly S. pneumoniae which is the case for beta lactams and even more for macrolides which exposes the patients to complications of their infections.

Also, resistance is of concern for non-respiratory-tract infections and bystander effects are also to be taken into account. We have started seeing a decrease of susceptibility of enteric pathogens to antibiotics that are used to treat both respiratory-tract infections and non-respiratory-tract infections, namely serious enteric gram-negative infections, which is really alarming, as well as the selection of C. difficile strains resistant to the quinolones that are hypervirulent strains responsible for high morbidity and even mortality.

[Slide.]

In this context of resistance, the three main attributes of telithromycin are of paramount importance. It is active against key respiratory bacterial pathogens, common and atypical pathogens. It is active against antibiotic-resistant S. pneumoniae.

It has a novel dual binding mechanism. There is low level of resistance to telithromycin of S. pneumoniae, less than 1 percent. It has limited activity against non-respiratory pathogens, namely enteric gram-negative.

In fact, telithromycin is the only antibiotic that carries all these features at the same time.

[Slide.]

In community-acquired pneumonia, telithromycin shows high efficacy. That is important because that is the most severe indication. It included patients with multi-drug-resistant S. pneumoniae as well as patients at risk of complications such as the elderly, patients with bilateral pneumonia,

patients with pneumococcal pneumonia.

I think this is really a premise that needs to be kept in mind; these drugs showed activity in the most severe of the respiratory-tract infections. Efficacy was also supported by Phase IV studies that are summarized in the briefing documents in countries of a high level of S. pneumoniae resistance.

[Slide.]

In acute bacteria exacerbation of chronic bronchitis, telithromycin showed that it was consistently clinically effective in all studies versus a broad range of comparators. But, more than that, confidence in efficacy was also obtained by analysis of patients at risk of complications such as patients with risk factors of morbidity, patients with airway obstructions for example. These are the most difficult to recruit in placebo trials.

Recently completed Phase IV studies also support this efficacy in particular in patients with S. pneumoniae resistance with favorable result

versus macrolides.

[Slide.]

In acute bacteria sinusitis, telithromycin showed that it was consistently effective when it was tested against treatments recognized for their efficacy. Here, again, when we look at efficacy in the subgroup of interest, the patients that are with either severe infections, according to the investigators, or documented pathogen at entry, or total opacity on sinus X-ray, or patients with more than seven days of symptoms or more than 10 days of symptoms, telithromycin still was very effective in those patients.

So, at this stage, I think that we have accumulated a certain amount of data in the subgroup of interest to support the efficacy of telithromycin in those patients.

Recently, we have also--further to the discussion that was held here regarding time to symptom resolution, we performed two studies including a score that we have developed with psychometric validation. This has not been still

filed to the NDA but it goes in the same direction showing that telithromycin is as effective and even better in one study which was an open trial versus Agmentin but still with good efficacy in time to symptom resolution.

[Slide.]

What about the risks? The first thing is that they were assessed extensively both in clinical trials and in postmarketing experience. There has been evaluation of the postmarketing reports repeatedly with additional measures to better evaluate adverse events of special interest.

There has been analysis of reporting rates, data-mining analysis with several methods and two large epidemiology studies which were performed to evaluate the hepatic risk.

[Slide.]

Each antibiotic has a specific safety profile. We think that the safety pattern of telithromycin has been well characterized. Some of the events are common to other antibiotics. Some are specific to telithromycin.

Most side effects are gastrointestinal. Some rare serious adverse events have been reported with the use telithromycin, myasthenia gravis exacerbation, which can be life-threatening. Rare severe hepatic events were reported postmarketing but which appear to be comparable to other antibiotics in the two large epidemiology studies presented, infrequent syncope, uncommon mild to moderate visual events, reversible, which is almost a fingerprint of telithromycin.

Those events can be rarely severe. There has been no documented sequelae. There is a minimal QTC prolongation possible with no evidence of increased cardiac risk.

The other classes of antibiotics have different safety profiles. Beta lactams are known to be associated with anaphylactic shocks, or C. difficile infections for the cephalosporins, or hepatotoxicity for Augmentin.

Quinolones have been associated with anaphylaxis, QTC prolongation, tendon rupture and also hepatotoxicity. The macrolides are associated

with QTC prolongation, serious liver injury, hepatotoxicity.

Overall, we believe that the safety/risk with telithromycin appears comparable to widely prescribed antibiotics using the same indication.

[Slide.]

I would like to move now to what have been the communications of these risks and what could be additional communication tools that we think could be used.

There have been several labeling updates including patient package-insert updates which have been implemented. Communication included more recently a Dear Healthcare Professional letter. Healthcare professional organizations such as the Myasthenia Gravis Foundation were contacted. A Ketek website is available for healthcare professionals and also for patients and includes information on the risks with telithromycin.

We support continuous medical education. Members of the Speakers Bureau are updated swiftly with labeling changes and the same applies to slide

kits and the sales force are trained.

[Slide.]

In addition to these actions, we think that the change to the new package-insert format will improve the communication to the patients. We think that we can have more targeted healthcare communications using a neurology alert, adding patient chart stickers for myasthenia gravis which is a simple thing to do, which we can certainly do.

We can contact specific myasthenia-gravis centers of excellence. Currently, we thought that we were close to the last Dear Healthcare Professional letter sent to see the effect of this letter on the myasthenia-gravis prescriptions but we think that we can have more targeted actions there.

For patient education information, we can add additional alerts regarding adverse events of special interest on the website. We are currently evaluating packaging options to distribute patient information or a mitigation guide.

We will continue having interaction with

myasthenia-gravis organizations and we are trying to monitor the frequency of the use of Ketek among myasthenia-gravis patients. We have just started a study through a case-match tracking of pharmacy claims, treatment and medical claims.

[Slide.]

So, in conclusion, telithromycin has a unique antibacterial spectrum focused on respiratory pathogens. It includes common and atypical pathogens and multi-drug-resistant S. pneumoniae. It has limited activity on enteric gram-negative pathogens. It has been consistently effective in all clinical trials in respiratory-tract infections including the most vulnerable patients.

Phase IV data, preliminary Phase IV data, provides for the support for this efficacy. The overall risk associated with telithromycin appears to be comparable to widely used antibiotics used in the same indication. In particular, two large epidemiology studies show comparable risk of severe liver injury versus antibiotics used in

respiratory-tract infections.

We believe that telithromycin is an important treatment option for its approved indication, community-acquired pneumonia, acute exacerbation of chronic bronchitis and acute bacterial sinusitis.

I would like to thank you for your attention.

DR. EDWARDS: Thank you, Dr. Leroy. We need to now move on to the FDA. Dr. Rosemary Johann-Liang will give a summary for considerations of risk and benefit.

FDA Presentation

OSE Summary Considerations of Benefit and Risk

DR. JOHANN-LIANG: I know it has been a long morning, but it is still morning. So good morning.

[Slide.]

I am Rosemary Johann-Liang from the Division of Drug Risk Evaluation. In our division, our daily job is to evaluate postmarketing drug safety. In the end, however, to ultimately

drug-risk evaluate, we must take into account what benefit the drug offers in treating disease in order to put the risks incurred with the drug in perspective.

My task is, then, to summarize the overall risks and benefits of telithromycin for the committee's considerations.

[Slide.]

The question for your discussion and deliberation is, based on the evidence, does the benefit of Ketek outweigh the risk from Ketek. We want you to consider this question for each of the three currently approved indications separately.

Please keep in mind that we approve drugs which is a medical intervention on a human being based on diseases, not organisms. Please also keep in mind that, since this is an already approved product, we are here to reassess and readdress the evaluation of evidence.

The question has been brought out about other drugs. We will tackle that step-by-step, as you heard Dr. Jenkins yesterday. But for today, we

are focusing on the evidence available for Ketek. Does the evidence of benefit outweigh the evidence of risk based upon what we know now as we close the Year 2006.

[Slide.]

Just as a frame of reference for you to use as I go through my summary talk. I want to orient you to the overall scheme of how we evaluate evidence in clinical interventions to see whether it would warrant an approval as a clinical therapeutic.

When we evaluate safety, we are generally analyzing the data and gathering a totality of evidence about harms of the drug. We look at biological plausibility of harm, animal-study signals, signals from clinical pharmacology studies, adverse-event data from clinical trials, postmarketing safety reports, observational studies, epi studies, et cetera, the totality of evidence of harm.

Occasionally, we are fortunate to be able to test a safety question in a randomized and

controlled large safety trial such as Study 3014. Study 3014 was set up to look at Ketek versus Augmentin in a comparative, prospective manner.

Unfortunately, as you have heard, the results of that study are not usable. Thus, we are left with uncertain measures and opinions about how to resolve the uncertain totality of evidence of harm.

On the other hand, when we look at efficacy, the law tells us that we need substantial evidence. Substantial evidence is based on results from adequate and well-controlled trials. Hypothesis testing in clinical trials is performed to specifically provide substantial evidence of benefit. Evidence must show that the medical intervention has been translated to therapeutic benefit for patients.

[Slide.]

This is the outline that I will follow. First, we will summarize the salient points from the discussions that we have heard in the last one-and-a-half days. I would like then to put the

risks discussed regarding Ketek in perspective showing you data on antibiotic use, other oral antibiotics with similar use and their risk profiles including cumulative exposure and, lastly, point out to you, based upon the most appropriate antibiotic comparators, why Ketek is notable in its toxicity.

Next, I would like to summarize what we know now in the Year 2006 regarding how we look at substantial evidence of benefit when evaluating efficacy of the drug. I will summarize the issues with noninferiority trial design.

We will then briefly summarize the efficacy data on Ketek for the three indications under discussion, has substantial evidence been shown.

Lastly, we will have a slide or two summing up risks to benefit of Ketek.

[Slide.]

As you have heard, the Ketek risks highlighted in OSC presentations are; hepatotoxicity, visual toxicity, loss or

disturbance of consciousness, exacerbation of myasthenia gravis.

With the labeling update in June of this year, hepatotoxicity and exacerbation of myasthenia gravis appear in the Warnings Section of the Ketek labeling. Vision toxicity and loss of consciousness appear--actually syncope--appear in the Precautions Section of the label.

Currently, there is no box warning or medication guide available. We have heard a lot of numbers regarding these adverse events throughout the presentations. You have also heard the methodological issues using passive surveillance data to generate quantifications of risk, whether domestic U.S. or from foreign sources.

Due to the imperfect methodology, there remain differences in interpretation of the quantification of these adverse events. However, I think we would all agree that all four highlighted Ketek risks have a clinical nature which are striking; that is, the sudden time to onset and the rapid tempo of these adverse events.

What this means is that when the drug is ingested by the patient, we cannot really mitigate risk with any confidence. The only way to mitigate the risk is to define the population up front that would benefit from taking the drug to treat the disease that justifies the potential risks.

[Slide.]

I wanted to show you this slide. This was a point of discussion yesterday. Dr. Graham had come up and discussed these person-time analyses with you. I just told you that we have so many methodology issues with passive-surveillance data, et cetera, and one must be circumspect in looking at numbers across different time spans with different drugs to treat different diseases.

Given that, however, I show you this slide, this is a slide compiled by Dr. David Graham, to illustrate what I just said about the clinical nature of Ketek adverse reactions, the rapid onset of the clinical toxicity of hepatotoxicity.

When you look at reporting rates by

person-time analysis rather than just number of prescriptions as a measure of exposure, Ketek's rate is in the range of those drugs recently restricted or withdrawn for hepatotoxicity.

Ketek is an oral-only drug given for short duration, five days, you have heard, to treat outpatient respiratory infections. The reporting-rate analysis by person-time illustrates the time at risk for liver injury with Ketek occurs very early. The risk is stacked right up front, as Dr. Graham discussed yesterday.

Dr. Brinker, yesterday, showed you the data that the median time to onset was four days for the acute liver-failure cases that he showed you. One other point from this slide is that Ketek's acute liver-failure risk, which is approximately 170 per million person years, is markedly increased over the background rate, about 1 per million person years even before we factor in under-reporting and regardless of whether there was stimulated reporting.

[Slide.]

Moving on to the other three highlighted Ketek risks and the clinical nature of toxicity, please recall that, for the average reactions of loss of vision or blurry vision, et cetera, the concerning operative word from a drug-risk assessment perspective is the word "sudden," sudden loss of vision, sudden blurry vision.

Dr. Wassel showed you the data that, in more than half of the cases reporting time to event, vision loss or blurry vision occurred on the first day of therapy, within an hour or two of dosing.

A similar tempo for the adverse-reaction umbrella category of disturbances of consciousness, of those reporting, over 70 percent had onset within the first day of therapy and mainly with two hours. Again, the operative word is "sudden," sudden loss of consciousness.

For exacerbation of myasthenia gravis brought on by Ketek, we see a clinical picture that, again, is the rapid tempo of adverse reactions with 70 percent of the cases occurring

with onset after the first dose with median time of 1.25 hours.

I remind you of the serious outcomes that these patients experienced; respiratory failure, intubation and even death.

[Slide.]

Next, I would like to turn to putting the risks that I have summarized for you regarding Ketek in perspective. I want to show you this slide. It is very busy. It is a pie chart. This data comes from Carol Pamer on drug-use specialist work, using the Verispan Physician Drug and Diagnosis Audit, or PDDA. This is a monthly survey that monitors disease states and the physician intended prescribing habits on a national level.

This is the most recent complete annual data from 2005 looking at the top ten ICD-9 three-digit diagnosis codes associated with U.S. drug uses for oral antimicrobials.

You can see that the leading diagnosis that physicians are checking off to give oral antimicrobial therapy are relevant to our

discussion; respiratory-tract infections. Please note that, instead of ABS, though, it is chronic sinusitis here. Please note that that, instead of AECD, it is bronchitis non-otherwise specified here.

Please note that there is a large area of the pie here that says, "all others," that we will spend some time on in another discussion when we talk about judicious use of antibiotics.

[Slide.]

The next point of reference then is what drugs are being prescribed. This pie chart is, again, the 2005 annual data. This pie encompasses the total dispensed U.S. retail prescriptions for oral antimicrobials using the Verispan Vector 1 national, or VONA, database.

VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions.

Carol Pamer, again, has broken down for us the drug classes of oral antimicrobials. You can

see that the top four classes of antimicrobials prescribed are the penicillin-derivative beta lactams followed by macrolides, then cephalosporins and quinolones, the point of our discussion.

[Slide.]

Just to put the risk of Ketek in perspective, the other oral antibiotics that are used to treat similar indications are represented here. This is not a comprehensive list but a representative one of frequently used antibiotics by the classes of antimicrobial products that was shown to you in the pie slide.

The meaning of the purple background for the three boxes will become clear as I walk you through the logic exercise in the next slide.

[Slide.]

I previously summarized for you the four highlighted Ketek risks which appear in the drug-labeling Warnings and Precautions Sections. This is a display of, again, the four classes of antibiotics and what we know about their risk profiles taken from the Warnings and Precautions

Section of the current drug labeling.

For beta-lactam antibiotics, both penicillin-derivatives and cephalosporins, the top two concerns are anaphylaxis/hypersensitivity and pseudomembranous colitis from Clostridium difficile. In Augmentin labeling, there is also an additional warning regarding hepatic toxicity.

For macrolides, again, pseudomembranous colitis is highlighted with more emphasis on hepatic dysfunction and drug-interaction issues which can lead to serious cardiac adverse outcomes.

For fluorquinolones, there is a whole array of toxicities including CNS, neuromuscular, cardiac and hypersensitivity issues. As you are aware, gadifloxacin was withdrawn this year due to dysglycemic toxicities. Oral therapy with levofloxacin and moxifloxacin continue to be used for outpatient respiratory-tract infections.

However, it is important to note that these fluoroquinolones have intravenous dosage forms and are indicated for severe CAP as well as for a variety of inpatient indications. The most

recently approved fluoroquinolone, gemifloxacin which is only available currently in an oral dosage form, have more issues with cutaneous skin reaction and does have an additional paragraph under the Precautions Section in the current labeling.

[Slide.]

I promised you the meaning of the colors. Remember that I had said that drug risk can only be put in perspective when we know the benefit or, actually, the margin of the benefit would be even better offered by the drug.

Likewise, drug risk for an individual drug in the postmarket setting can only be put in perspective in consideration of what the relative drug-risk profiles are of drugs that are available to treat similar diseases.

We need to be cautious, however, in that we choose appropriate comparators. To say how does Ketek compare to all the other antibiotics is not an appropriate approach. We want to drill down to the most appropriate risk-profile comparators but accounting for similar indications, similar dosage

forms and similar drug exposures in postmarketing.

This slide addresses the drug-exposure variable. I have tabulated for you, based upon Carol Pamer's work, the cumulative U.S. exposures of the antibiotics that we have been talking about from January of 1995 through June of 2006, a span of 10.5 years.

This data, again, comes from the work done by Carol Pamer using the VONA database. The drugs in green have seen much larger exposures due to the fact that they went to market a long time ago. These are older antibiotics that we have a better understanding of their toxicity profile.

The drugs in purple have less exposures because these are relatively newer drugs. I show you the year of approval in parentheses for each of the newer drugs. New drugs translates to less exposure marketing which, in turn, translates to less certainty of toxicity-profile understanding from any us.

Please note that, even among these four newer drugs, the exposure numbers extracted are

variable with the order of magnitude difference between Spectrasta or Factive to Ketek or Avalox.

[Slide.]

Finally, the last slide in the color drill-down exercise. This is a table modified from Evelyn Farina's work in her review of gemifloxacin for the recent advisory meeting that was held three months ago.

This shows you that, for the four drugs listed as newer drugs in the slide before, moxifloxacin is different in that this antibiotic has both I.V. and P.O. dosage forms and is indicated for more serious diseases which often need inpatient treatment. Thus, in the end, we are left with the three antibiotics in purple as the most appropriate side-by-side comparators when assessing what is know about their toxicity profiles postmarketing.

These are cefditoren, an oral cephalosporin approved in 2001, with four indications of AECB, CAP, tonsillar pharyngitis and uncomplicated skin and skin structure infections.

gemifloxacin, an oral fluoroquinolone with only two indications, AECB and mild to moderate CAP approved in 2003 and telithromycin, an oral ketolide approved in 2004 for ABS, AECB and mild to moderate CAP.

[Slide.]

Cefditoren's safety profile appears thus far to be similar to well-known and characterized safety profile of the class of cephalosporins. However, since the postmarket exposure of this drug in the U.S. is relatively small, our uncertainty about new or evolving safety signals remains high for this drug and we will continue to monitor.

This committee had a chance to hear about gemifloxacin extensively three months ago at the ADAC Advisory. Gemifloxacin's safety profile is like others in the class but with the increased frequency of cutaneous reactions, particularly in young females. The commission voted that, for ABS, given no evidence of efficacy provided by the N.I noninferiority trials, the risks incurred were not justified.

Subsequently, the applicant withdrew the supplemental NDA. For Ketek, the safety profile appears to have similarities to the macrolide class issues like special senses, liver, possibly Q.T., cardiac, et cetera.

We have already summarized the Ketek risk profile for you. However, Ketek stands out among the macrolides and, as the first ketolide, in its unique and notable toxicities. The vision toxicity with Ketek is unique. It is not seen in other antibiotics that we know of. Although it has been said that it is rare, that it is 1 percent in clinical trials, when you project that to the population that will see the drug, 1 percent in a million--and you can do the numbers.

The rapid onset of clinical manifestations of other highlighted adverse reactions are notable, as I have stated before.

[Slide.]

So, in summing up, Ketek risk in perspective. The four highlighted risks; hepatotoxicity, exacerbation of myasthenia gravis,

visual toxicity and disturbances of consciousness. You can see that these are the rapid and sudden clinical toxicity manifestation is what we are concerned about.

Once you ingest the drug, you cannot really mitigate the risk. Again, the only way to mitigate the risk is to define the person who really needs the drug up front. We must define the population with the diseases who would benefit and understand as much as we can how much benefit from the drug that would justify the potential risks from taking the drug.

We want to approve drugs that work for these diseases.

[Slide.]

Enough about summary of risk for the moment. Let's turn to summarizing efficacy. Remember this organization scheme I showed you at the beginning. How do we assess efficacy to determine the benefit from medical intervention so that it actually is shown as a medical therapeutic. Unless the assessment of harm, which is usually by

the totality of evidence, the examination of efficacy evidence, as defined by law, must be through substantial evidence.

[Slide.]

What is substantial evidence? FDA published regulations on criteria that define substantial evidence in 1970. U.S. District Court finds that Congress intended specific definitions of substantial evidence and did not mean it to be opinion-based.

Substantial evidence is not because the guidelines say so. Clinical practice in which the guidelines are used come after substantial evidence has been shown. Clinical trials proceed clinical practice. For medical intervention, substantial evidence means data from adequate and well-controlled trials not individual interpretations.

Substantial evidence applies to both serious and life-threatening diseases as well as less-serious diseases.

[Slide.]

The question that follows, logically, is then what is adequate and well controlled. Conveniently, this is defined for us in 21 Code of Federal Regulations 314.126. There are seven criteria which need to be met for a clinical trial to be adequate and well controlled in order to provide substantial evidence of benefit of the drug, the medical intervention.

In regards to our discussion, I will focus on Criteria No. 2. However, noninferiority trials have issues with all seven criteria. This will need in-depth discussion in the future. I mean, every one of those requires a lot of time as we discuss how to design better trials, how to design superiority trials.

Right now, however, it is this No. 2, the issue of a control where the problem mainly lies when attempting to provide substantial evidence for diseases with high spontaneous resolutions such as upper respiratory-tract infections.

[Slide.]

The issue is quantitation of control.

Clinical trials compare outcomes with drug to what would have occurred without drug. This is why, in clinical trials, we us a concurrent control as a comparator, usually a placebo or a sugar pill.

For active control trials, it does not have a concurrent negative control, a placebo. We need to do some homework beforehand. We need reliable and reproducible previous data that show a benefit of the active control over placebo which have suitably conservative margin based on examination of the whole confidence interval, not just point estimates.

For noninferiority trials, which is an active controlled trial without a concurrent negative control, we need to select an active comparator which has reliably and clearly shown in previous trials to have a benefit or a placebo by a certain margin. Remember that noninferiority trials are not testing whether two drugs are equal.

Noninferiority trials are designed to show that the new drug is worse than the control drug by a certain margin. Therefore, the margin of benefit

that the control has over the placebo from previous adequate and well-controlled trials must be clearly established and quantified as per the ICH-E9 document as shown here.

[Slide.]

So what is the problem? I want to digress for a second and give you a personal story. So this is on me, not on the FDA. I came to the agency six years ago exactly and started as a medical officer in the Office of Antimicrobial Products. My first NDA was a supplemental NDA for AECB for one of the fluoroquinolones going from seven days to five days.

This was put on my desk. Because I am a pediatric I.V. person, I didn't really know what AECB was. So, in looking through the application of acute exacerbation of chronic bronchitis, I was struck at how many of the patients in that application were 18-year-olds, 18-year-old smokers.

I began to ask, well, why is everything coming out 80 percent. No matter which way you look at it, all the point estimates with the spread

comes out 80 percent, whether you are young, old, whatever. So the issue goes as to--over and above the issue of control with noninferiority, the issue of who is coming into trials, the inclusion into the trials, and the way we measure outcome, who is going out of the trial. All these things really need substantial discussion.

This is an understanding in progress. This has been a learning curve for all of us. I did not understand what noninferiority testing was at that time.

But once you do understand, once you begin to understand what this means, that this is not really providing substantial evidence, then we must move on, as Dr. John Jenkins said yesterday. The problem is No. 2 of the seven substantial evidence criteria.

I am now back on record for FDA. For active controlled clinical trials with noninferiority design, the design does not assure benefit that tests drug over placebo in diseases with high spontaneous resolution such as ABS and

AECB. Due to the problem of the quantitation of control, we need well-established and reliable data from previous placebo-controlled trials to establish a quantifiable margin of benefit.

[Slide.]

Let's look at this graphically. We have heard from a number of hepatology experts during this meeting and lots of other experts provided by Sanofi-Aventis. When it comes to clinical trials for antimicrobials and particularly in the area of noninferiority-trial design, I think we would all agree that Dr. Powers is the expert. I am borrowing the expert's slide here from his recent presentation at the gemifloxacin advisory.

On this slide is the current noninferiority trial testing the new drug against the control. So that is on the left side, the current trial. Remember that noninferiority means no worse than by a certain margin to an older drug. So that shows you there is the control and there is a test, no worse by a certain margin.

In order for that older drug to be a

control that delineates drug effect over the natural history of resolution of disease, there has to be a preservation of effect of the control over placebo shown from previous past trials which are adequate and well-controlled.

There has to be this margin that just goes across that the control preserves over the placebo. In non-antibiotic trials of upper respiratory-tract infection, the way it is currently designed and studied and the way we are currently looking at them, this placebo is actually not down here but actually we think up here.

[Slide.]

So let's look at Ketek specifically. I populated these tables directly from the numbers given in the Division of Anti-Infective and Ophthalmologic Products briefing package to the committee. We are looking at AECB and ASB Ketek Phase III trials here with response rates for Ketek and control in the per-protocol population.

Notice that there is some variability of these response rates around the 80 percent mark.

Remember what I said about everything comes out around 80. But the variability is across studies not within each study.

The response rates are remarkably similar for Ketek and control for each of the studies for AECB and ABS. So the question is if there had been a third arm in each of these trials, a concurrent negative control, which would measure the natural history of disease resolution, where would that response lie?

[Slide.]

Graphically, what we are seeing with the numbers in the previous slide, is control and test just around the 80 percent response. If we were to take the control and ask, what is the margin of benefit over placebo, where would that be?

We are concerned because that placebo, or the natural history of the resolution of these respiratory diseases, as we look at them now and we want to do better, is most likely up here, as shown here, and not down below as shown in the previous slide in the beginning.

Further, due to the biocreep of endpoints over successive antibiotics being approved by worse margins, we are concerned that the placebo effect may actually be higher than the drug compounded by all the toxicities that we have heard about regarding all the different antibiotics. Therefore, this is placebo going up.

It is important to point out that the issue of all the response rates coming out similar also has to do with problems of the other substantial evidence criteria, as I said, such as who goes into these trials, inclusion criteria, what and when the outcomes are measured, et cetera, all-comer trials, the majority of which do not have bacterial disease and then measuring response rates at test of cure, way out, 10 to 21 days. In high-risk natural-resolution diseases all contribute to everything looking the same, new drug to old drug to natural history.

[Slide.]

This is an incredible body of work by Dr. Powers et. al which was presented at the 2005

Interscience Conference on Antimicrobial Agents in Chemotherapy. This is the analysis of all placebo-controlled trials available in the literature on AECD, not selected studies because all studies have flaws in this issue.

What we are looking for is consistency and reliability across all the trials so please follow with me. Each of the branches on this tree are individual placebo-controlled trials from the literature. So, going to the left favors the new drug. Going to the right favors placebo.

If we are setting up a noninferiority margin of 10 percent or above, which is what has been done with these antibiotic trials, then we will want to see all these branches reliably and repeatedly lining up above the 10 percent margin, all over there. Right? Over there left of the dotted line that came for you.

You can see that graphically this is not so. Not only do these lines not line up on the left of the 10 percent, they cross zero for many of these studies.

[Slide.]

So what has been happening? We have got to talk about something regulatory, from the regulatory perspective. I just highlight for you here the major regulatory discussions, both internally and externally, that has been happening regarding AECB and noninferiority issues. Really, it starts with Dr. Susan Thompson's presentation in February of 2002 where I first started to understand this process as well.

This committee met to discuss noninferiority margins for antibiotics to treat infectious diseases including AECB. So this has been going on for a while. November of 2002, IDSA, PhRMA, FDA Working Group meeting, further discussion. You have heard about the January '03 ADAC on Ketek because this was one of the indications.

In April of 2003, Factive receives NDA approval for AECB, mild to moderate community-acquired pneumonia, still all a noninferiority-trial design. In April of '04, this

drug receives approval for AECB, ABS and mild to moderate CAP. I want to point out to you that that is the last approval for AECB, this drug, based upon noninferiority trials because, of all these issues that have come up.

But sponsors have continued to submit antibiotic trials using noninferiority-trial design to the agency. So, because of that, it went to an internal regulatory briefing in July of '05. In that regulatory briefing, and I was there, personally, but I am pulling this from the minutes and I am quoting. "Is there a scientific basis for continuing to base approvals for AECB, AECOPD on noninferiority trials?"

The panel said, and I quote, "Based on current data, the panel believed there is not a scientific basis for noninferiority trials in acute exacerbation of chronic bronchitis given both the lack of historical evidence of sensitivity to drug effects and issues with defining both these and lack of appropriate clinical outcome measures.

"Trials should be done as superiority

trial designs. The panel asked about other disease indications where these issues with noninferiority trials have arising, and the discussion included trials in acute otitis media and acute bacterial sinusitis where these same issues apply."

[Slide.]

The second question, "Are there precedents where superiority trials were successfully performed where there is reported resistance by sponsors of clinicians to performing these trials. How were these trials moved forward?"

Regulatory briefing panel response; "During the late 1990s, the Director of Anesthetics, Critical Care and Addiction Drug Products encountered years of significant resistance from industry before sponsors finally agreed to switch from conducting noninferiority clinical trials to placebo and active controlled trials in situations where sponsors submitted formulation changes of existing opiate products. This is important for antibiotic therapy, too.

"It is important to note that, when such

trials were undertaken, it was discovered that some of the products did not prove to be more effective than placebo substantiating the concerns regarding noninferiority trials. The panel emphasized that, as science changes, the standards for regulatory approval also must change to reflect what we have learned. In this case, AECB, the data pointed to the lack of information on which to base noninferiority trials."

[Slide.]

I want to move on to ABS. This is, again, the body of work that was done by Dr. Powers et al. regarding ABS from placebo-controlled trials that have been reported in the literature. He presented this data at the recent gemifloxacin advisory meeting.

For the sake of time, I don't want to go through the whole thing. But, again, it shows you a delta margin of 10 percent which is what is really used--10 or 15 percent are what is used--for ABS noninferiority trials. All the branches do not line up reproducibly and reliably on the left of

the margin. It actually crosses the margin, crosses the zero leaving no margin of benefit.

[Slide.]

Again, I want to walk through with you some highlights of ABS and its noninferiority regulatory time line. Skipping through some of these public discussions, because you have heard it already, some of these most recent antibiotic approvals for ABS based upon noninferiority are formulation changes. You are going from 5 days to 3 days, 7 days to 5 days, very similar to what was discussed in the regulatory briefing regarding AECB and the addiction products.

The last approval for ABS was Levaquin for five days for ABS and that was in August of '05 because, finally, in September of '06, three months ago, so you can see that the actual regulatory actions for ABS take some time to get there. In September of '06, this ADAC on Factive, gemifloxacin, voted not in favor of ABS based upon noninferiority.

The question posed was, do the safety and

effectiveness data presented demonstrate an acceptable risk/benefit profile of Factive for the 5-day treatment of patients with acute bacterial sinusitis. The vote was 11 to 2 in favor of negative.

[Slide.]

So efficacy of Ketek. All clinical trials leading up to approval of Ketek for ABS, AECB and CAP were noninferiority trials with greater than or equal to 10 percent noninferiority trials you sort of set up front. Response rates in the 80 percent range, the result was spread similar to both Ketek and controls.

So the questions for you regarding AECB and ABS are, "Has substantial evidence of drug efficacy via adequate and well-controlled studies standard been shown when the drug has been assessed exclusively in noninferiority setting."

"Did these noninferiority trials provide substantial evidence that the use of Ketek added any benefit over and above the natural history of the disease?"

Superiority-trial designs have been recommended by members of this committee three months ago at the Factive Advisory in ABS in order to prove with substantial evidence that taking the drug benefits the patient and, therefore, is worth the risk of adverse reactions.

[Slide.]

We have to spend a few slides on CAP. The original benefit shown for pneumonia was with severe disease with endpoints of mortality. Ketek is indicated for mild to moderate outpatient or, as Dr. Bartlett called it, walking pneumonia only.

So the margin of benefit is less clear. However, I think we also heard that this is a less spontaneous resolving disease. There is probably a preservation of efficacy margin for study in the noninferiority setting.

But, then, it is the issue of resistance. It is really a paradox, what we hear, because, on the one hand, Ketek's claim is for treating resistant pathogens, particularly macrolide-resistant pathogens.

What this implies is that Ketek is superior to older drugs which are ineffective against resistance pathogens yet all trials were preformed as noninferiority, no worse than the older drug. Therein lies the conundrum.

We heard a lot about medical need. Yes; we do have a medical need. We really want to approve good drugs. That is what we are all about. We want to review evidence. But true medical need is that we need to demonstrate the evidence that Ketek or other antibiotics is superior to older drugs if the claim is that you are better for resistant pathogens.

[Slide.]

Activity is not the same as efficacy. Preclinical in vitro and animal data provide hypotheses upon which clinical trials of antimicrobials are based, on people. In vitro and animal models alone do not define substantial evidence.

I quote from a recent sort of paper from CID. "Recent studies that have assessed the impact

of beta lactam and macrolide resistance on clinical outcomes in CAP fail to provide incontrovertible evidence for a direct link between in vitro resistance and treatment failure."

I quote Dr. Townsend from the most recent advisory, who is sitting here. He said, "A couple of people on the panel have made the comment that, 'so regardless of what the clinical trials have shown, that in vitro data are convincing enough that they feel comfortable that this drug would be efficacious for the treatment of acute bacterial sinusitis.' I just want to say that I am pretty uncomfortable with that approach. If all we need are in vitro data, there is really not much point in doing clinical trials, at least for efficacy."

[Slide.]

So the risk to benefit ratio of CAP, hard to quantify with exact numbers for outpatient CAP treatment with Ketek for the reasons that I have told you. Certainly, superiority trials, even in this indication, that demonstrate that patients will with resistant pathogens in this disease being