DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE (AIDAC) MEETING

Tuesday, March 4, 2003

8:00 a.m.

Marriott Washingtonian Center
Grand Ballroom
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LEGGETT: Good morning. Welcome to the Anti-Infective Drugs Advisory Committee. We are here today to talk about Factive, gemifloxacin tablets.

We will go around the table and introduce ourselves. One little piece of information I would like you to try to remember is these mikes--only four of them can be on at one time so, after you are done talking, please remember to switch it off.

Let's start down there.

Introductions

DR. ALBRECHT: Good morning. I am Renata Albrecht, Director of the Division of Special Pathogens and Immunological Drug Products.

DR. COX: Good morning. I am Edward Cox, Deputy Director, Office of Drug Evaluation IV.

DR. TIERNEY: Maureen Tierney, medical officer, Division of Special Pathogens, FDA.

DR. BRADLEY: John Bradley, Division of Infectious Diseases, Children's Hospital, San Diego.

DR. PORETZ: I am Don Poretz in private practice of infectious diseases in Fairfax,

Virginia.

DR. PATTERSON: Jan Patterson, Infectious Diseases, University of Texas Health Science Center, San Antonio.

DR. O'FALLON: Judith O'Fallon, statistician, Mayo Cancer Center Statistics Unit, Mayo Clinic, Rochester, Minnesota.

DR. RELLER: Barth Reller, Infectious Diseases, Clinical Microbiology, Duke University Medical Center.

DR. RODVOLD: Keith Rodvold, professor at the Colleges of Pharmacy and Medicine, University of Illinois, Chicago.

DR. TURNER: Tara Turner, executive secretary for the Committee.

DR. LEGGETT: Jim Leggett, Infectious Disease, Health Sciences University at Oregon and Providence Portland Medical Center.

DR. WALD: Ellen Wald, Pediatric Infectious Diseases, University of Pittsburgh School of Medicine.

DR. CROSS: Alan Cross, Infectious Diseases, Center for Vaccine Development, University of Maryland.

DR. PROSCHAN: I am Mike Proschan. I am a

statistician at the National Heart, Lung and Blood Institute.

DR. GLODE. Mimi Glode, Pediatric Infectious Disease, Children's Hospital at the University of Colorado, Denver.

DR. BIGBY: Michael Bigby, Department of Dermatology, Harvard Medical School and Beth Israel Deaconess Medical Center in Boston.

DR. EPPS: Roselyn Epps, Chief, Division of Dermatology, Children's National Medical Center, George Washington University.

DR. ADKINSON: Franklin Adkinson, Allergy and Immunology, Johns Hopkins School of Medicine.

DR. HILTON: Joan Hilton, Biostatistics, University of California at San Francisco.

DR. CONJEEVARAM: Hari Conjeevaram, Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor.

DR. SJOGREN: Maria Sjogren, Gastroenterology and Hepatology at Walter Reed Army Medical Center.

DR. LEGGETT: Thank you.

I think we will start the morning first by Tara with the conflict of interest statement.

Conflict of Interest Statement

DR. TURNER: Thank you. The following announcement addresses the issues of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest in this meeting with the following exceptions:

In accordance with 18 U.S.C. 208(b)(30, Dr. James Leggett has been granted a waiver for his pending consulting for a competitor on an unrelated matter. He will receive a fee of less than $10,001.

Dr. Celia Maxwell has been granted a waiver for her speaker's bureau and possible membership on an advisory committee for a competitor on unrelated matters. Her fees are less than $10,001.

Dr. Lynn Drake has been granted a waiver for her role as a member of an advisory board for a competitor on an unrelated matter. She receives a

fee of less than $10,001 for this activity.

Dr. Ellen Wald has been granted a waiver for her employer's contract with a competitor on an unrelated matter. Funding received is less than $100,000.

Dr. Jan Patterson has been granted a waiver for her role on the speaker's bureaus for two competitors on related matters. She receives fees of less than $10,001 for these activities. Dr. Patterson has also been granted a waiver for her memberships on an advisory board and a visiting professor program for two competitors on unrelated matters. She receives fees of less than $10,001 for these activities. Finally, Dr. Patterson has been granted a waiver for her spouse's consulting for a competitor on an unrelated matter. Her spouse receives a fee of less than $10,001 for this activity.

Dr. John Bradley has been granted a waiver for his role as a consultant for two competitors on unrelated matters. He receives fees of less than $10,001 for these activities.

Dr. N. Franklin Adkinson has been granted a waiver for his role as a consultant for two competitors on unrelated matters. He receives fees

of less than $10,001 for these activities.

Dr. Keith Rodvold has been granted a waiver for his role as a consultant for two competitors on unrelated matters. He receives fees of less than $10,001 for these activities.

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

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr. Kenneth Brown is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Brown reports that he owns stock in Johnson & Johnson and Pfizer. Dr. Brown also serves as a consultant to Wyeth.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from such involvement and their exclusion will be noted for the record.

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

DR. LEGGETT: Thank you. I think we will begin with opening remarks by Dr. Renata Albrecht. I would like to remind all speakers to try to stay on time. At the end of each presentation we will take one or two major questions and save the rest of the questioning to sort of do as a group at the end of each particular session before the break. Dr. Albrecht?

Opening Remarks

DR. ALBRECHT: Thank you, Dr. Leggett.

[Slide]

Good morning, everyone. On behalf of the Division and the Office I would also like to add my words of welcome to everyone for today's session of the Anti-Infective Advisory Committee during which we are going to be talking about the fluoroquinolone gemifloxacin.

First of all, however, I would like to

thank the members of the committee, as well as the consultants and guests, for taking time from what we know are your very busy schedules to join us for these discussions and to provide us with your advice. I would also like to thank the applicant, LG Life Sciences, as well as their agent, Parexel International, for their willingness to bring this application to the committee, and their cooperation in providing additional information in preparation for this meeting and, of course, our staff in the Division and the Office who have worked very hard despite unexpected adversities, like the blizzard of 2003, to try to put this advisory committee together. Finally, let me acknowledge Mrs. Karin Klunk and Dr. Yon Yu for their invaluable help in making the handouts that you all have available and running the presentations for the FDA this morning.

[Slide]

Let me go ahead and turn to some basic comments and try and give you a perspective of how we reviewed this application, and the thoughts that were going through our minds as we planned for this advisory committee.

As you are very well aware, the fluoroquinolone drug class is not a new one. Many

drugs in this class have been developed, submitted to the agency and, in fact, approved. We also have examples of ones that have not been approved or after approval, withdrawn, limited in scope and so forth.

[Slide]

Over time we have learned a great deal about the efficacy of this class and we know that as a class it does work in a broad range of indications. We have, of course, also learned quite a bit about the safety profile and, again, as a class fluoroquinolones are labeled with various contraindications, warnings, precautions and adverse reactions in their product labeling. As might be expected, each fluoroquinolone presents its own unique characteristics and, in making regulatory decisions on these issues, we have, in fact, brought some of the fluoroquinolones to this advisory committee for input. The most recent examples include moxifloxacin and levofloxacin.

[Slide]

What about gemifloxacin makes us bring it to you for your input and for your deliberation? What are the unique aspects that we wish you to provide us advice on?

Clinical studies with gemifloxacin have actually demonstrated that gemifloxacin is not inferior to the FDA approved comparison in the indications of community-acquired pneumonia, acute exacerbation of chronic bronchitis and, in fact, a couple of indications that we will not be talking about at length today.

[Slide]

As far as safety, clinical studies have demonstrated that the incidence of rash is somewhat higher in the gemifloxacin arm than in the comparator arm, and this was found for the study population as a whole and also in specific subsets, most notably in females under the age of forty.

[Slide]

This is the only data that I will be showing for the introduction. This is actually a slide that I have borrowed from Dr. Maureen Tierney's presentation and you will see it again when she gives the full safety presentation later this morning. This demonstrates the gender and age relationship of rash.

If you look on the X axis, at the left-most corner the bars represent the incidence of rash in control patients. Moving from left to

right are different durations of gemifloxacin therapy, ranging from 3 days to 5, 7, 10 and 14 days. The Y axis represents the percent of rash reported by patients. If we look at the color coding for the bars, the blue bars are males greater than 40; the purplish ones are males under 40; the white ones are females greater than 40; and these light turquoise are females less than 40. As you examine the graph, I think you can appreciate the increased rate of rash reported by increasing duration of therapy and, again, in the light turquoise bar the relatively higher rates of rashes in women under the age of 40.

So, as you listen to the detailed presentations by both the company and FDA you will learn more both about the safety profile and the efficacy profile of the drug product.

[Slide]

Let me also add that before the company presentations and the FDA presentations, we are actually truly fortunate to have Dr. Michael Bigby, from Harvard, join us to give a presentation about adverse cutaneous reactions to drugs to give you more background on these reactions in patients. That presentation will then be followed by Dr. Jonn

Powers, from the Office of Drug Evaluation IV, who will be speaking about Strep. pneumoniae and resistance in that organism.

Dr. Powers' presentation is applicable to today's advisory committee because the company has asked us to consider penicillin-resistant and other resistant Strep. pneumo. as part of the indications, but I think it is also a preview to tomorrow's advisory committee which will talk at length about resistant organisms and topics relevant to that.

So, having mentioned some of the issues that we have been considering regarding gemifloxacin, what is it that we are going to be asking of you today? I think the questions that we will be posing to you come in two categories. One, we will be asking you about the risk-benefit considerations as far as the approval of gemifloxacin. The second is risk management considerations.

[Slide]

We will be asking actually three questions. Dr. Goldberger will review these in much greater detail during the charge to the committee this afternoon, but we wanted to give you

just a brief overview of the type of advice we will be seeking so that you will keep this in mind as you hear the presentations.

The first question will basically be to ask whether, based on the data you have heard and your clinical and scientific opinion, the benefits of gemifloxacin therapy outweigh the risks for the proposed individuals with community-acquired pneumonia and acute exacerbation of chronic bronchitis.

[Slide]

The second question, assuming the answer to the first one is yes, will be to ask you to give us some thoughts about the type of information that should be provided to physicians and patients, also your suggestions about caveats on what patients should receive gemifloxacin and any discussion on either risk management or risk communication strategies that you might find useful.

[Slide]

Just to complete the questions we ask, if the answer is no, what additional information you would recommend be obtained for either or both of the indications.

So, with those remarks, I will turn it

back to you, Dr. Leggett.

DR. LEGGETT: Thank you. Dr. Bigby, could you please help us out?

Adverse Cutaneous Drug Reactions

DR. BIGBY: Good morning.

[Slide]

What I thought I would try to do in the half hour allotted is to just talk basically about adverse cutaneous reactions to drugs and try to keep it mostly focused on the questions that have been raised about gemifloxacin.

[Slide]

These are the common drug rashes, exanthem, urticaria and fixed-drug eruption. By far, drug exanthem is the most common adverse cutaneous reaction to drugs. Its description I think is important and very germane to the discussions that will occur here today. It is generally a fine, papular eruption, meaning that patients develop very small, 1-3 mm bumps on the skin that have generally a sort of erythematous, quite pink color. They are often numerous. They generally start on areas of trauma so that in ambulatory patients most commonly you see that the rash starts on the legs and will spread up from

there. In patients that are hospitalized, on their back, often the rash will begin on their back and spread from there. It can be quite localized as well as quite generalized. It is commonly mis-described as a macular eruption or a maculopapular eruption but, in general, most patients that get rashes from drugs have this drug exanthem.

Urticaria is a lot less common but is the second most common reaction and those lesions are hives. It is basically an area of edema in the skin. Almost always there is associated redness or erythema. Fixed-drug is actually irrelevant for today's discussion so I will skip it.

[Slide]

I think this is one of the major concerns that has been raised about this drug and whether or not it could potentially be a cause of more serious drug reactions. The three serious drug reactions are toxic epidermal necrolysis, Stevens-Johnson syndrome and what is called a drug hypersensitivity syndrome.

TEN and Stevens-Johnson syndrome are probably a spectrum of the same disease in which patients develop full thickness necrosis of the

epidermis that leads to blister formation, sloughing of the skin and, depending on the area of involvement, is quite serious and has a mortality rate up to over 50 percent in some studies for TEN. The mortality from Stevens-Johnson syndrome is much less. Luckily for all of us, this is a very infrequent reaction and in the best estimates available for drugs that have been well studied the rate is somewhere around 0.5 to 1.0 cases per million of exposures.

An important thing and a question raised about this drug is whether or not one could go from one of these, exanthem or urticaria, to something more serious. I would say that there is no evidence that that transition occurs, and I think it is not something that is described or that one would in general have to worry about.

[Slide]

The drug hypersensitivity syndrome is similarly rare. The rash associated with it is the exanthem that I have already described. Patients also have fever, hepatitis, they are very ill, almost always wind up hospitalized, usually in intensive care units, and the mortality rate is actually quite high. There is a lot of controversy

about how such patients should be handled.

[Slide]

When a patient develops a drug eruption, how do you know what is responsible? It is basically done in the majority of clinical cases by the timing of the rash; some knowledge about how commonly drugs cause rash; what happens when you withdraw the drug; and usually in this country what happens if patients are accidentally rechallenged to the drug. Deliberate rechallenge is something that is rarely done here but is done actually fairly frequently, particularly in experimental studies in Scandinavia.

[Slide]

In general, the drug exanthem and urticaria occur within the first 3 days after a drug is started. There are several very notable exceptions to this, again germane to our discussion today, that can occur up to 2 weeks after a drug is started for many antibiotics and allopurinol. This means that actually you can have the drug given for 1, 2 or 3 days, stop the drug and people can develop drug eruptions 2 weeks later, or if they are continually treated for that duration of treatment, 2 weeks, you will often see or not

infrequently see drug rash develop late. In fact, I was struck by looking at the figures on onset of rash for this drug that it really paralleled a lot of the eruptions that we observed when we did a study trying to determine rates of reactions to drugs based on consecutively monitored hospitalized patients, and I will show you some of that data as well.

[Slide]

In terms of getting actual rates of drug reactions, I published in June of 2001 a systematic review of available studies looking at rates of reactions to drug. The kind of data that is available--the best is prospectively collected data on monitored patients. These were very big studies that were conducted between the late '60s and mid to late '80s. There are also data from retrospective studies, usually based on computerized medical records. Lastly, there are some data, not quite as useful, on spontaneous reports and consumption of drugs. Again, I will show you some of that data.

[Slide]

I did some assessment of the quality of the studies, and the best studies had well-defined,

representative samples and sufficiently long and complete follow-up. It was clear how the researchers linked drug reactions and the drug. The temporal relationship was correct and you could calculate rates based on the data provided, as well as their 95 percent confidence intervals.

[Slide]

Not to bore you with a lot of numbers, but this is data collected on something like 38,000 patients. I am just presenting rates for drugs that were more than 1 percent and were taken by more than 1000 patients. The only point I want to make here is that in this list of things that produce rashes more than 1 percent of the time, the list is dominated by antibiotics, with the exception of transfusions, and amoxicillin and ampicillin are very high up on the list and I think those are drugs that were used as comparators for gemifloxacin. So, we are talking about comparators that actually have very high rates of cutaneous reactions. I think you should pay some attention to the rate number because I think these are really pretty much the most accurate estimates of how frequently drugs cause rash. For amoxicillin and ampicillin it is around 5 percent in the real

world.

[Slide]

This one I will skip. But, you know, that study also generated a list of drugs that hardly ever cause rashes but I don't think that is germane for this talk.

[Slide]

This is a study that was done in Switzerland in three teaching hospitals. Again, roughly 40,000 patients were monitored. Estimates were made for rates at which drugs cause rashes and, again, the big take-home point is that antibiotics predominate. They have rates over 1 percent, and the aminopenicillins were among the highest reactors. The estimates here are pretty comparable to what we obtained in the BCDSP, so a reaction rate of 5 percent or higher for the aminopenicillins is something that you want to have stuck in your mind.

[Slide]

More recently fluoroquinolones were studied. This data was based on about 19,000 patients. It was retrospectively collected on the basis of computerized records. You will notice again that the fluoroquinolones were the highest

reactors relative to amoxicillin and Augmentin, which is a combination drug. The rate is considerably lower than what I showed you on the previous slides and I think it had to do with the methodology involved.

It is interesting, there was a study done in Italy based on spontaneous reports and consumption that showed that there was marked variability in the rate at which specific fluoroquinolones produce rashes, and some produce rashes as much as three times as others in that same class. So, it is not a uniform class of drugs in terms of the rates at which they produce reactions.

[Slide]

I think this may be the last data slide. This is from a study of about 15,000 patients based on pediatric records. I only include it to show you that with more recently introduced antibiotics, like Cefaclor, you can pick up a signal for them causing rashes. Again, the rash rate for Cefaclor is actually quite high, higher than the sulfonamides in this study.

[Slide]

In summary, the common exanthem producers

are on this slide, predominated by antibiotics. The aminopenicillins are high on the list and fluoroquinolones certainly have lately gotten onto the list of common exanthem producers.

[Slide]

The drugs that can produce urticaria are similar. In addition, histamine releasers like contrast dye and morphine by directly causing histamine release, can cause urticaria.

[Slide]

This is irrelevant.

[Slide]

The drugs that cause TEN and Stevens-Johnson syndrome, with the exception of sulfonamides, is a pretty different list of drugs and you don't see those antibiotics, most of which we will be talking about today, on this list of drugs that are associated with TEN and SJS. I am actually not aware of any sort of big signal having been detected in terms of fluoroquinolones producing either TEN or Stevens-Johnson syndrome.

[Slide]

For the drug hypersensitivity syndrome, again, sulfonamides are the one antibiotic that is associated but it is mostly the anti-seizure drugs

that are deemed responsible for most cases.

The last thing I would like to say is that in a randomized, controlled trial it is actually a fairly rare thing to pick up a signal of frequent drug rash production, and when you do pick up such a signal in a randomized, controlled trial it is almost always clinically relevant when the drug is introduced into the market.

That is the end of what I had to say. I am happy to answer questions.

DR. LEGGETT: Thank you, Dr. Bigby. Only one or two questions. Yes, go ahead, Donald.

DR. PORETZ: Can you explain, in these two different charts that you gave us, one with the BCDSP and one with van der Linden et al., the difference in reaction of skin rash? Amoxicillin in the BCDSP was reported as 5.1 percent and 1.2 percent in the other. That is a huge difference.

DR. BIGBY: Yes, it is actually not such a huge difference in that it is entirely a question of methodology. The methodology in the BCDSP study is that it was a funded study. Patients who were hospitalized were monitored by a group of nurses who followed the patients through the course of their hospitalization and they were looking for all

adverse drug reactions, including skin reactions. So, the ascertainment of the numerator, the number of patients who had rashes, and the denominator, the total number of patients exposed to any and every drug was very high. So, I would say that among the data that I have shown you the BCDSP data and the data from the teaching hospitals in Switzerland is the most accurate.

On the other study you referred to where the rate was 1.2 percent the data were collected from electronic medical records in which the patients developed a rash and were also reported to have been exposed to the drug. Charts were pulled and reviewed on that basis, and I would say that the ascertainment of patients that had rashes would only have occurred if they saw a physician and the physician wrote down that they had a drug reaction, which I would say in general would be a very small minority of the actual patients who had rashes because most patients, if it is just a little bit of a rash, won't report it to a doctor.

So, I think that the difference is solely explainable on the basis of the methodology and the 1.2 estimate is probably much lower than the reality.

DR. RELLER: When one is doing a drug study, like the one being presented today, do you think that would reflect the potential highest chance of having rash or a lower chance?

DR. PORETZ: No, that is why I actually made that closing statement. I think if you pick up a signal in a randomized, controlled trial the actual use rate will be much higher.

DR. LEGGETT: Dr. Reller?

DR. RELLER: For the clinical indications that we will be discussing, co-trimoxazole or amoxicillin which you gave rates for are used in adults; doxycycline as well which is perceived, especially with sun exposure, to be a source of cutaneous reactions. Do you have any data from your studies as to where doxycycline would fit into the spectrum of frequency that you shared with us?

DR. BIGBY: I don't remember which but in one of the slides tetracycline had a rate of 1 percent relative to the amoxicillin which was about 5 percent. I mean, if you want a number I would say it would be 1 percent or less.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: I just had a question on your slide, Table 5, about the fluoroquinolones.

Was there a time period where the fluoroquinolones seemed to produce the rash? Was it early on, within the first 3 days, or was it usually later, after a week or so, that the rashes were seen that were reported here? The reason for the question is that in the drug that we are looking at, gemifloxacin, the patients seemed to develop the rashes as they took more of the drug, so later on in the course as opposed to earlier. So, I wanted to know if that sort of thing was seen for the fluoroquinolones that were reported here, or if that is even known.

DR. BIGBY: The two places that fluoroquinolone data were prominent were the van der Linden study and the study by Naldi that looked at spontaneous reports and consumption. Off the top of my head, I don't remember that that phenomenon was discussed by either one. But I also know from a lot of the other data and also from BCDSP data that late onset rashes with antibiotics was actually a fairly common pattern and I don't find it at all surprising.

DR. LEGGETT: Dr. Cross?

DR. CROSS: I would like to ask a question on methodology in terms of cross-sensitization,

which we will address later on. Assuming that we challenge with a drug that initially caused a rash but does not 100 percent of the time cause a rash on subsequent rechallenge, how does one assess the capacity for cross-sensitization between, let's say, the drug under discussion and another fluoroquinolone?

DR. BIGBY: Well, I think I am going to avoid answering this question because I don't have any data upon which to base an answer.

DR. CROSS: But is there any methodology that one uses? For example, early on in my training we were told that if one reports a sensitivity or allergy to penicillin, if you then rechallenge that patient with a cephalosporin you would expect to see a rash about 10 percent of the time.

DR. BIGBY: Yes, that is actually a bad example because I think that that figure in that data is actually totally incorrect. But what you are asking about is drugs in the same class, and if you want my opinion about it, I would say that if a patient developed a rash to a fluoroquinolone they should never be given another one because I think that the rate of reaction that you would get in

that scenario is unacceptably high. I mean very high, unacceptably high. For example, if somebody developed a drug reaction to a cephalosporin, I think that probably in the real world it would preclude the use of another cephalosporin for that patient unless you had no choice.

DR. CROSS: So, a rechallenge would have an unacceptably high--

DR. BIGBY: Right, for a drug in the same class, yes.

DR. LEGGETT: Dr. Rodvold?

DR. RODVOLD: My understanding is there are like two rashes. You can get it more acute but then there is also like an ampicillin-related rash that kind of accrues later in the course of therapy?

DR. BIGBY: No. The only thing I would say about that is that in general, with the exception of antibiotics and allopurinol, almost always when you get a drug exanthem it occurs in that first 3-day window. For many antibiotics and allopurinol and actually some of the anti-epileptic drugs you can see drug reactions as far out as 2 weeks after the drug starts. It is not a separate entity; it is the same drug reaction. It can occur

in that 1-3-day window and it can occur all the way out to 14 days. That data is very, very clear and very reproducible so it is not an unusual phenomenon.

DR. LEGGETT: Two questions. In general clinical practice the word of mouth is sort of that if you have an allergic reaction to penicillin you shouldn't get it again. But we all know that if someone got a rash to penicillin 30 years ago you can give it again orally and oftentimes nothing happens. Indeed, some of the data here suggests that when people got a second exposure they did not get a rash. So, how ironclad is that and what is the mechanism of exanthem? Do we know? Are there sort of memory half-lives that then subside?

DR. BIGBY: There have been a lot of studies on the clinical predictability of history of drug allergy and the general result is that the history of drug allergy has very little predictive value because what people remember from 30 years ago often wasn't a drug reaction at all. So, I think that the explanation of why somebody can say they had a rash to penicillin 40 years ago and then you give it to them with impunity is that if you actually have the data from 40 years ago it was not

a drug reaction, and if they really had a drug reaction to penicillin the likelihood that they would have a reaction again is very high.

DR. LEGGETT: My second question, do you know of any IgE-mediated allergic responses to fluoroquinolones?

DR. BIGBY: There is almost no sort of hard data knowledge about the pathophysiology of the drug exanthem, although everybody involved in drug eruptions thinks that it is an immune complex disease. Urticaria, on the other hand, is thought to be predominantly an IgE-mediated disease, and off the top of my head I don't remember what percentage of the rashes to fluoroquinolones were urticaria but I know it is in here.

DR. LEGGETT: Thank you. Dr. Glode?

DR. GLODE: I just have a quick question about the methodology of the Boston Collaborative Drug Study. Since I work mostly in inpatient medicine I have never seen anyone on only one medicine. So, if you were receiving amoxicillin and were on pheno. barb. and got a blood transfusion and developed a rash, was the methodology such that the best attempt was made to ascribe it to just one or did you put it in all

three columns?

DR. BIGBY: No, no, no. The methodology here was actually quite creative and it was sort of made up by Herschel Jick. There is no standard way to do this. What he did at first blush was that for every drug we had graphs of counts of patients developing rashes after the drug was started. So, you had a graph of that for every drug and you had a sort of mean reaction rate as well as a confidence interval for that drug. What he did, and I thought it was actually brilliant, was as a first cut of the data just to take drugs that had reaction rates more than twice the sort of overall average rate, and also a pattern where the reactions occurred within the first 3 days after the drug was started, and those drugs were just sort of arbitrarily identified as high rash producers. Then, once you had those, you eliminated that from the data set and then you looked at the rest of the drugs, and you did this in progressive stages. Then, at the end, to answer your question, the average number of drugs each patient took was 9, and to settle those cases where there was more than one high rash producer what you did was to divide the cases proportionally. For

example, if the rate for ampicillin was 5 and for tetracycline was 1 and there were 6 such patients, you gave 5 of them to ampicillin and 1 to tetracycline. So, that is how it was done.

DR. LEGGETT: One final question. Mike?

DR. PROSCHAN: I was wondering if the late onset rashes are more serious than the early ones.

DR. BIGBY: As far as I know there is no correlation.

DR. LEGGETT: Thank you, Dr. Bigby. I would like to take this moment to have folks who arrived late introduce themselves.

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

DR. DRAKE: Lynn Drake, from Massachusetts General Hospital Harvard Medical School.

DR. BROWN: Ken Brown, representing industry, University of Pennsylvania.

DR. MAXWELL: Celia Maxwell, Howard University.

DR. POWERS: John Powers, lead medical officer for antimicrobial drug development in ODE IV.

DR. LEGGETT: Are you ready to go?

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Streptococcus Pneumoniae

DR. POWERS: What I would like to talk to you about today is a continuation of a discussion that we began back in the January committee meeting. At that time, the sponsor for that drug requested an indication for community-acquired pneumonia and a few other diseases due to penicillin-resistant Streptococcus pneumoniae and macrolide-resistant Streptococcus pneumoniae.

Today the drug sponsor is requesting an indication that includes both those two resistance patterns and cefuroxime-resistant Streptococcus pneumoniae as well. So, this seemed like a good opportunity to actually discuss where we are going with antimicrobial resistance in Streptococcus pneumoniae and its implication for prescription drug labeling.

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What I would like to talk to you to start off about is our historical background on how we have approached antimicrobial resistance labeling claims in the past, and then to try to tie together what we have seen has been done in labels in the past with some rationale of why we have done what we have done, then present some data to you that we

have acquired on cross-resistance among Streptococcus pneumoniae strains of various antimicrobials, and then put forward for the committee a proposal for future labeling of antimicrobial resistance claims for Streptococcus pneumoniae.

As Dr. Albrecht said, this discussion is relevant to this drug today because of what the sponsor is requesting but it really does also dovetail very well into tomorrow's discussion on drug development for antimicrobially resistant pathogens.

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If we look back at the labels that the FDA has issued in the past, most of these drug resistance claims deal with resistance to drugs within the same class which we have termed "in class" resistance. This would include things like a number of cephalosporins for beta-lactamase producing organisms like Haemophilus influenzae and Moraxella cetarrhalls in various infections. The label for nafcillin also reads for severe and serious infections in penicillinase-producing staphylococci.

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On the other hand, the FDA has not granted several claims for "out of class" resistance, meaning resistance to a class outside of that particular drug class, such as in the past when fluoroquinolones were asked for indications for penicillinase-producing Neisseria gonorrhoea infections. That has been denied. As well as there are no labels that include beta-lactamase producing H. influenzae or Moraxella catarrhalis in the quinolone labels.

On the other hand there are approved "out of class" resistance claims and here are a couple of examples. For example, vancomycin is indicted for serious or severe methicillin-resistant Staph. aureus infections and, more recently, linezolid was approved for hospital-acquired pneumonia and complicated skin and skin structure infections with methicillin-resistant Staph. aureus, and also carries a claim for vancomycin-resistant Enterococcus faecium infections. Dalfopristin-quinupristin also carries an indication for vancomycin-resistant Enterococcus faecium bacteremia. Then, most relevant to our discussions today, levofloxacin and now, last Friday, moxifloxacin are both approved for

community-acquired pneumonia with penicillin-resistant Streptococcus pneumoniae.

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Well, what ties all these together, the "in class" and the "out of class" resistance? What are we trying to do when we grant a resistance claim? Really, the benchmark is that the information in labeling should aid clinicians in their ability to make clinical decisions and in choosing drugs to treat their patients.

We have divided this up into five characteristics that would enable a clinician to make that decision. The first is that the organism is unique and distinguishable. In other words, is there cross-resistance across drugs such that one cannot differentiate between these organisms? For instance, if we look at vancomycin and methicillin resistant Staphylococcus aureus we know that MRSA organisms are resistant to a number of other drug classes, including the quinolones, and yet we don't grant separate indications for methicillin-resistant Staph. aureus and quinolone-resistant Staph. aureus.

Secondly, the drug to which organism is resistant is commonly used to treat the infection

under study. For instance, we don't grant indications for, say, streptomycin-resistant gram negative rods for urinary tract infections because people don't use that drug to treat that particular infection.

The third thing is that there are few alternative therapies to be able to treat that drug [sic] and that is why this information is important to put in the labels so that the clinicians know that this particular drug is available to treat that kind of infection.

The fourth thing is that in vitro resistance actually correlates with increased clinical failures, and we had a long discussion about this at the last advisory committee meeting related to macrolide-resistant Streptococcus pneumoniae and the state of the data there.

Finally, the other important thing is that allowing a drug sponsor to put a resistance claim in the label provides incentive for that sponsor to actually acquire data on the efficacy and safety of the drug in infections due to that resistant organism.

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Let's apply these principles and look at

some of what we have done in the past to see if this makes sense. For vancomycin and MRSA, MRSA clearly is a unique and distinguishable organism with different characteristics but, as I said, methicillin resistance correlates with resistance to other drugs which are not separately designated in the label. For instance, resistance to cephalosporins and resistance to quinolones are not given separate designations in addition to methicillin resistance.

At the time of approval, methicillin and other anti-staphylococcal penicillins were commonly used, as they are still commonly used today, in the treatment of staphylococcal infections although methicillin itself has fallen out of common usage. At the time of vancomycin approval there were few alternative therapies for serious methicillin-resistant Staph. aureus infections and some data, although this is controversial, indicate worse outcomes with methicillin-resistant Staph. aureus compared to methicillin sensitive Staph. aureus infections and, certainly, if one receives a drug to which the organism is resistant the outcome appears to be worse.

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Now let's apply this to levofloxacin and penicillin-resistant Streptococcus pneumoniae. At the time of approval, penicillin-resistant Streptococcus pneumoniae was considered a unique, new organism for which clinicians desired treatment information.

Penicillin was a previously commonly used antimicrobial to treat community-acquired pneumonia, and also penicillin resistance is used in clinical laboratories as a marker for resistance to other drug classes as well. In these organisms that are resistant to many drug types in Streptococcus pneumoniae there appear to be limited treatment options and I am going to show you some data on the cross-resistance amongst these various types of classes.

At the time of levofloxacin approval there was very little data in the clinical literature on outcomes with community-acquired pneumonia in people who were infected with penicillin-resistant Streptococcus pneumoniae.

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But since that time we have acquired some information on the cross-resistance patterns of penicillin-resistant isolates and their resistance

to other drug classes. Also, there is accumulating clinical data that the outcome in patients who are infected with penicillin-resistant Streptococcus pneumoniae is no worse in most cases of community-acquired pneumonia as long as the minimum inhibitory concentration to penicillin of that infecting organism is less than 4 mcg/ml, which is the majority of PRSPs in this country which have less than 4.

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Before I go on to present some data about cross-resistance among various antimicrobial classes for Streptococcus pneumoniae, one could ask the logical question of what degree of cross-resistance among drug classes is clinically significant.

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When you try to look this up, there is actually little scientific data that actually addresses this question of at what degree does this become relevant. The Infectious Disease Society of American guidelines for some infections suggest that clinicians should use alternate drugs when resistance is 10-20 percent for a drug class. The IDSA guideline for community-acquired pneumonia

doesn't address this question but the one for urinary tract infection does specifically say 10-20 percent. However, this is based on expert opinion, not really data.

But since the time that that IDSA guideline was issued, one model based on a cost estimate, estimated that this clinically relevant degree or resistance to the drug trimethoprim-sulfamethoxazole, which is commonly used in urinary tract infections--when that level approaches 22 percent, then that becomes clinically relevant at least in terms of how much cost is spent and it didn't really address it in terms of what the clinical outcomes are as well. So, one could actually say perhaps that that level of 20 percent could be used as a benchmark, although that still remains controversial.

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Since the January advisory committee we have been trying to get data on the cross-resistance patterns amongst various antimicrobials for purposes of drug development. We obtained a contract to get surveillance data from Focus Technologies for the purposes of identifying and tracking resistant organisms of

public health importance for drug development.

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The surveillance network of Focus Technologies encompasses 317 U.S. laboratories. They are directly connected via computer to these laboratories and it is updated continuously. This surveillance includes community, government and university laboratories and includes hospitals that have bed sizes from less than 99 to 500 beds. The surveillance network gives us access to greater than 65 million antibody susceptibility testing results, and these are not active surveillance but they are based on cultures which the clinicians order. There are greater than 500 microbial taxa included in this and susceptibilities to greater than 100 individual types of drugs. This covers almost 3 million patients in the United States and includes both inpatient and outpatient data.

The data I am going to show you today is pooled information although we are planning on separating this out into inpatients and outpatients once we have a chance to look at the data in more detail. This gives us access to about 2.6 percent of all isolates tested per year in the United States, and some of the other surveillance programs

are actually less than 1 percent.

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What I am going to show you now is a couple of graphs on cross-resistance. This is a blank slide to show you what we are trying to look at here. So, what we have done is to look at one drug and show increasing MICs across the X axis compared to a second drug with increasing MICs across the Y axis. What you will see here is some red dotted lines, here. These vertical lines, here, are the intermediate susceptibility breakpoint for drug X, and the second vertical line will be the breakpoint for a high level resistance to this drug, X. The two horizontal lines are the intermediate susceptibility breakpoint to drug Y, and this higher dotted horizontal line will be the high level susceptibility breakpoint to drug Y.

What this will do is divide this up into nine different boxes. Some of these drugs don't have intermediate susceptibility breakpoints so you will see that some of these boxes are missing when I show you some of these. But what we will have then is that in the lower left-hand corner will be organisms that are susceptible to drug X and susceptible to drug Y. In the upper right-hand

corner you will see organisms that are resistant to drug X and resistant to drug Y. This diagonal line, here, will be organisms that are concordant, meaning they are either susceptible, intermediate or resistant to these two drugs and the rest of the boxes are discordant.

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What I wanted to show you was an example of an organism and two drug classes that we know are concordant. We know that most methicillin-resistant Staphylococcus aureus are resistant to quinolones as well. So, if we look here, across the X axis we have increasing MICs of oxacillin. The Y axis is increasing MICs to ciprofloxacin. This is a total of 234,000 isolates that are tested and, actually, these dots represent 10 results each because if we put them all in here the entire slide turns black. So, it is just to make it a little easier for you to look at. This vertical line, here, is the breakpoint for oxacillin to methicillin-resistant Staphylococcus aureus, and this is the intermediate breakpoint for cipro. and the high level breakpoint for cipro. They are a little off because when you shine these things up on Power Point all the lines move around

so this is the best we could do with this.

What I wanted to show you was that essentially when there is correlation in cross-resistance you can almost draw a diagonal line here, and you see that there is clustering of the organisms here, meaning that if this organism is oxacillin susceptible it also tends to be susceptible to ciprofloxacin. If the organism is oxacillin resistant, it also tends to be resistant to ciprofloxacin as well.

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Let's apply this to looking at Streptococcus pneumoniae, looking at penicillin and cefuroxime. Again we see the same kind of pattern here. There is a clustering in the lower left-hand corner which shows that if an organism is susceptible to penicillin it is likely to be susceptible to cefuroxime, and if an organism is resistant to penicillin it is likely to be resistant to cefuroxime as well.

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Let me show you the opposite of a lack of correlation. Here, if we look at penicillin on the X axis and levofloxacin on the Y axis you can see that if an organism is penicillin susceptible, it

tends to be susceptible to levofloxacin; if an organism is penicillin resistant we see the clustering in the lower right rather than the upper right. If there was a correlation between levofloxacin and penicillin resistance we should see the clustering up here, however we see it down here, meaning that penicillin organisms for the most part still retain their susceptibility to levofloxacin.

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We did this for any number of drug combinations, looking at resistance in Streptococcus pneumoniae, and we did this in two ways. First we took penicillin-resistant organisms and tried to see what their resistance was to other drug classes. Then we flipped it around and looked at it the other way and said let's take organisms resistant to the other drug classes and see how often they are resistant to penicillin, trying to make sure that the correlation goes in both directions.

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The first slide that I will show you is the first example for penicillin-resistant Streptococcus pneumoniae and we tried to look at

the rate of resistance to other drug classes. As you can see here, the rate of resistance of penicillin-resistant Streptococcus pneumoniae to second generation cephalosporins is almost 98 percent; trimethoprim-sulfa almost 88 percent; erythromycin 82 percent; tetracycline is about 46 percent; clindamycin 23 percent; third generation cephalosporins 98.6 percent and then levofloxacin 1.4 percent. So, if we say that cut-off point is about 20 percent we can say that clearly second generation cephalosporin, trimethoprim-sulfa, erythromycin and tetracyclines are above that line. Clindamycin and third generation cephalosporins is debatable, and levofloxacin is clearly below that cut-off.

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Now let's take it and turn it around the other way. Let's take organisms that are resistant to second generation cephalosporins and see how often they are resistant to penicillin. So, this becomes a clinically relevant question for clinicians. If I have resistance to one of these classes, how often can I use one of the other drugs?

You can see that the correlation really

goes in both directions. Second generation cephalosporins 60 percent; trimethoprim-sulfa 50; erythromycin 50 percent; and tetracycline is around 50 percent. Then you will see that these bottom three, when you start off with clindamycin, third generation cephalosporin or levofloxacin resistance the level of penicillin resistance actually shoots up. So, 50 percent of clindamycin-resistant isolates are resistant to penicillin; 93 percent of third generation cephalosporin-resistant isolates are resistant to penicillin; and a third of levofloxacin-resistant isolates are resistant to penicillin, leaving you not much of a treatment choice when we get down to a levofloxacin-resistant bug.

The other thing I want to point out to you is how often clinical laboratories actually test for these, which goes to sort of the idea of how often do people actually use these various drug classes. These numbers correlate to when a lab tested penicillin resistance and tested for that drug resistance simultaneously. You can see that 32,000 isolates were tested for both third generation cephalosporins and penicillin, but we get all the way down to less than 6000 isolates

tested in labs against second generation cephalosporins and penicillin.

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What do we make out of all this information? There was a discussion at the last advisory committee in January about labeling organisms to just say susceptible pathogens only. In other words, a label would read something like drug X is indicated for community-acquired pneumonia in susceptible strains of Streptococcus pneumoniae. But when we look at that, it actually doesn't address what we have been doing in the past with resistance labeling, and that is actually conveying some important information to physicians.

There are also a couple of other issues. If we do not grant these claims to other drugs that are approved in the future, it may place those drugs at an unfair competitive disadvantage. One can say, well, that wouldn't be the case if we went back to the levofloxacin label and withdrew the penicillin-resistant Streptococcus pneumoniae indication. However, from a regulatory perspective that is actually very difficult to do.

The other thing that is a real key issue here though is, is this information that would be

important to convey to clinicians that these organisms are not just resistant to penicillin but if you have an organism that is resistant to penicillin then it is going to be resistant to these other drug classes as well? Again, that is the benchmark we use, are we educating clinicians here?

The other point that is really important to keep in mind here is that this drug label is not just written for infectious disease specialists who may be well informed about these cross-resistance patterns; it is for all kinds of clinicians who may not have as much information on cross-resistance.

The other issue is that if we don't grant resistance labeling claims and just put susceptible pathogens only, this really gives drug sponsors no incentive at all to go out and acquire clinical data on treatment with these resistant pathogens.

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So, what do we see here? We see a high rate of cross-resistance among penicillin-resistant classes and other drug classes, including second generation cephalosporins, macrolides, tetracyclines and trimethoprim-sulfa resistance. Therefore, based on what we said about vancomycin

and MRSA, these organisms do not appear to be unique. If you have a PRSP organism it is likely to also be resistant to these other drug classes as well.

The second criterion used is are these drugs commonly used in the infection under study? Yes, all 5 of those drug classes, penicillin, cephalosporins, macrolides, tetracyclines and trimethoprim-sulfa are commonly used to treat respiratory tract infections. It also conveys information about cross-resistance to clinicians in prescription drug labeling, especially because these drugs are often prescribed empirically. First of all, we don't always even get cultures in outpatients but, even so, we usually prescribe these drugs empirically for at least 48 hours when we do get culture information. Again, it also provides an incentive to the sponsor to obtain clinical information on treatment of these multi-drug resistant organisms.

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So, the proposal that we would put before the committee today, which would apply to this drug under discussion today but also to future drug labeling claims as well as going back to previous

drugs and changing their labels, would be to define a term called multi-drug resistant Streptococcus pneumoniae, similar to what we did with multi-drug resistant tuberculosis.

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Not to say this is how scientists and authors should define this, but for the purposes of drug labeling we would define this as resistance to penicillin, second generation cephalosporins, macrolides, tetracyclines and trimethoprim-sulfa. Doing this would maintain the distinct nature of non-cross-linked resistance such as that to the pneumococcal quinolones. So, that would be a separate indication as well.

This definition could change over time. If other resistance does become linked, we could go back to those labels and add in more things to this definition of multi-drug-resistant Streptococcus pneumoniae. This serves the purpose of informing clinicians that the organism is not just resistant to one drug class but is resistant to all of these drug classes where, if we designate them separately such as PRSP and MRSP, clinicians who are not informed in this area may assume that an MRSP still might be susceptible to penicillin. However, drug

sponsors would still need to obtain clinical data to garner this resistance claim.

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But are we raising the bar here by doing that? Actually, we are not. We are trying to streamline drug development by doing this. For example, a drug sponsor would need the strongest supportive data for "in class" resistant strains because that is what we are really worried about.

Let me give you an example. Suppose someone came in with a tetracycline type drug. They would need the strongest supportive data on tetracycline-resistant organisms. But does that mean they need a whole lot of penicillin-resistant organisms, macrolide-resistant organisms, etc.? Well, for "out of class" resistance one could make the scientific argument why should we be worried that this drug wouldn't work if the mechanism of resistance is different than that particular drug class?

The other thing is that from what I showed you we already know that a good proportion of, say, the tetracycline-resistant organisms are already going to be resistant to penicillin, second generation cephalosporins, macrolides and

tetracyclines so if they had a good number of tetracycline-resistant organisms they would already have a good number of isolates that were resistant to these other drugs as well in their database.

The other benefit of "out of class" resistance is that one may be able to use susceptible isolates to support the data on resistant isolates. For instance, we know that for, say, the anti-pneumococcal quinolones for the most part the MICs to penicillin resistant and penicillin susceptible isolates are pretty close. That would be a benchmark that we have to look at though, that there is no appreciable difference in MICs for penicillin susceptible and resistant isolates so that one could use the efficacy in penicillin susceptible isolates to support the penicillin resistant isolates for, say, a tetracycline type drug, given that alterations in penicillin binding proteins wouldn't have a whole lot to do with tetracycline afflux pumps.

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But this gets to another issue, and that is something that sponsors ask us all the time, how many do I need? The numbers game--my favorite. Sponsors love to have this number to shoot for when

they are garnering a resistance claim and this makes logical sense. If you are going to invest in a drug development program you want to know when you have won and when you have lost.

But it is not that easy when you are on our end and you have to actually review this clinical information, and we ask the basic question should resistance claims be based on quality of data rather than quantity of data? And, how would one define a high quality case?

Well, there are three things that we can think of. One would be that the disease is unlikely to remit spontaneously. For instance, if one looks at acute bacterial meningitis and you show that the drug works in meningitis, that is different than looking at, say, acute exacerbations of chronic bronchitis where the placebo cure rate in that disease may be as high as 50 percent.

The second thing we look at is the certainty of the diagnosis. Isolates from a normally sterile body site, like cerebral spinal fluid, tend to provide us more information than, say, isolates from a non-sterile body site, such as sputum.

One of the other things that is very

difficult, especially in serious disease, is that we look for little confounding in assessment of the drug's contribution to efficacy. Again, if we go back to, say, a meningitis trial and you show that you had 5 cases of meningitis and all 5 of them got better but then, when we evaluate the cases, we see that all these people got vancomycin and ceftriaxone and on day 5 they had new drug X added and on day 6 we raise the flag of victory and say, look, the patient got better and it is all because of drug X, that is very difficult for us to actually piece together.

Finally, there is the efficacy rate in the disease in question. So, if someone comes in with 5 cases of meningitis and four of them are failures and one of them was a success, what do we make out of that information?

So, when we talk about coming up with a number for sponsors to shoot for, what I am just trying to show you here is that it is very difficult to just draw a line in the sand and say X number of cases gets you an indication because it is really the quality that we are looking at as well as the number of cases.

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In conclusion, what I would like to leave you with is something for the committee to discuss here, again referable to this drug as well as to other drugs in the future, which is that an indication would read something like this: Drug X is indicated in the treatment of community-acquired pneumonia due to Streptococcus pneumoniae, including multi-drug resistant strains, meaning resistance to penicillin, second generation cephalosporins, macrolides, tetracyclines and trimethoprim-sulfa. Again, as we continue to gather information on this over time that definition of multi-drug resistance may change.

Then, what we would also suggest doing is listing the actual clinical trials data on which this resistance claim is based in the clinical studies section of the label. Therefore, if a sponsor studied more patients they would be able to show in the label that they had a stronger body of evidence than someone else did.

I will stop at that point and I would be happy to answer any questions.

DR. LEGGETT: Thank you, Dr. Powers. Dr. Poretz?

DR. PORETZ: Obviously, most physicians

are in practice and not infectious disease doctors. In different hospitals in the country you get reports of an antimicrobic sensitivity pattern that is either sensitive or resistant sometimes or MICs, depending upon the hospital or lab that is used. I have always wondered whether the average physician understands MICs. Is it confusing? Is it worthwhile reporting that? Actually, my microbiologist tells me it is cheaper, because it is automated, to do MICs than it is to replate sensitive or resistant. Does the average doctor know the difference? Does it make any difference in antimicrobic selection or is it confusing?

DR. POWERS: That is probably a question I am not qualified to answer. We have debated whether we should put MICs in the label or not. We have done so for some drugs. For instance, Augmentin does include an MIC in the label for where we think this drug is effective up to a particular MIC. So, we have done it.

Again, this is a tricky thing when you are writing a label. It doesn't mean that you should exclude information that an infectious disease physician might find helpful, but we should also write it in such a way that people who are not

infectious disease physicians can understand it as well. My personal opinion is that I agree with you, I don't know that the majority of non-infectious disease physicians would understand what those MICs actually mean.

The other point is that as far as labeling goes, we know that these breakpoints keep shifting around. For instance, the NCCLS just changed the breakpoints for third generation cephalosporins for non-meningeal isolates. So, that is a moving target for us as well.

DR. LEGGETT: Dr. O'Fallon?

DR. O'FALLON: Of course, I want to know are the MICs at one place the same as the MICs at the other place. So, do you have a problem with of shifting values?

DR. POWERS: That is a good point. After the last advisory committee meeting Dr. Leggett sent an e-mail showing how some resistant pneumococci were actually misidentified based on the methodology. So, we know that those things exist but that is why we went out and tried to gather this information with 317 different labs, trying to get a more broad-based approach to this.

DR. O'FALLON: This looks really good to

me, knowing what has been around here before, but putting a number in the label will be a problem unless the MICs are the same across the country.

DR. LEGGETT: Dr. Reller, could you address that point?

DR. RELLER: We recognize that laboratories, like clinicians, vary in their prowess but laboratories are very highly regulated and to be accredited, they are supposed to follow NCCLS standards and the numbers are very precise. They change because the science changes and an attempt is made, with documents coming out each January, to keep up with the science and change the breakpoints when additional data are available or clinical information about failures related to previous breakpoints.

The comments about how much information is conveyed with an MIC and automated methods in the laboratory--in reality most MIC reports from laboratories, in fact, are not MICs. They are based on breakpoint panels and they, in truth, convey no more information than an SINNR. There are few exceptions and I think, Dr. Poretz and all other infectious disease clinicians here, there are a few places where numbers are very important where

an exact MIC is crucial to care, like the less than 0.06 for penicillin in the treatment for meningitis with Streptococcus pneumoniae. But to get that precise MIC requires different methodology, actually doing an exact MIC which is not on automated system, through, for example, E-testing or other exact MICs. In the treatment for endocarditis an exact MIC to an infectious disease clinician for streptococcal endocarditis means something. There are a few situations where an exact MIC is necessary but most MICs on reports coming from clinical laboratories, in fact, are based on breakpoints and do not give any more additional information than an SINNR.

DR. LEGGETT: Thank you. Dr. Bradley?

DR. BRADLEY: I think that the vast majority of clinicians for the vast majority of infections look at the lab report to see whether the organism is interpreted as sensitive, intermediate or resistant. When interpretation of the breakpoints change, like what happened with enterococcus a few years ago and what just happened with the third generation cephalosporins, the understanding of why that change occurred is missing among the general clinicians. All they do,

they see that the bugs are now all intermediate or resistant or now, with the third generation cephalosporins in pneumococcus, a lot more susceptible.

So, I think the SINNR are critical pieces of information for the clinician and the NCCLS has done a very nice job of continuing to get new information to change the breakpoints if that becomes applicable.

The in vitro susceptibility, to go back to your initial point, John--our training is to look at in vitro susceptibility when we get an organism. When you approve a drug to treat that organism there is a disclaimer that treatment is based on in vitro susceptibility. So, the giving of special indications for organisms based on different in vitro susceptibilities doesn't make much sense and I think it has been used a lot for marketing as opposed to scientific usage in order to treat patients.

But the points that you make certainly are very well made in that there are a lot of resistant organisms that are present now, and for the doctor to know that it is the old-fashioned susceptible strain versus one that is tougher to treat,

susceptible versus multi-drug resistant, is a very interesting concept. In putting together your NDR for Strep. pneumo. I would suggest perhaps that you say resistant to penicillin plus two others because, as you mentioned, in addition to macrolides there are ketolides, oxazolidones and God knows what is going to come up next, and if you say it is resistant to all of them, then that actually represents only a very small percentage of all the resistant isolates, just the worse ones. Indeed, I think the concept you are trying to get across is the fact that there are some which have multiple drug resistance, not maybe to everything but to many, and to get drug approval and an indication in the label for those more resistant strains is quite reasonable.

DR. LEGGETT: Dr. Hilton?

DR. HILTON: I have a comment on your correlation plots. I like the comment at the end where you talked about the quality of the efficacy rate data, and I think it applies to the correlation plots. You mentioned that the data for those plots came from isolates that clinicians sent to labs. Of course, there could be multiple isolates from a single patient and they would

weight the findings by that patient's severity of disease.

DR. POWERS: That we ruled out. There are not multiple isolates per patient in this database. We took care of that. You do raise an important point though of who gets cultured. It may be skewed towards people that are sicker.

I will give you a good example. I am going to show some information on this cross-resistance for other types of organisms tomorrow when we talk about drug development. We looked at something like gonorrhea. I showed you that there are about 230,000 Staph. aureus in this database; there are 1500 Neisseria gonorrhoeae, which says that people aren't culturing for those. That doesn't mean it is not important; it just means people aren't looking.

No way did I mean to make this the be-all and end-all but it is the best thing we could get our hands around when we were trying to look at this problem.

DR. LEGGETT: One last comment. Dr. Brown?

DR. BROWN: John, that was a great presentation and I appreciate it.

DR. POWERS: Are you going to ask me what I think this time, Dr. Brown?

DR. BROWN: No, I am going to ask you for a very specific question, either you or Dr. Goldberger. The numbers game is very important to everybody. I think high numbers in the thousands of patients are important for assessing safety. However, for efficacy I think the numbers game becomes important and I would like to ask you, folks, if I had "wondermycin" and I was looking for a claim for penicillin susceptible or "wondermycin" susceptible pneumococcal pneumonia where I knew what the organism was either from a trans-trach. or a blood culture, I had X-ray diagnosis and I had a good cure rate, how many patients should I study to get that claim?

I have to tell you that more is not a sufficient answer, but that is the most common answer that we tend to get. As an example, when I was working up a drug for gonorrhea and we kept getting the answer more, and more, and more, we wound up studying a thousand patients with uncomplicated gonorrhea. That seems unreasonable. On the other hand, the number which we worked with at the time was in a given box, that is, one

organism by one disease, and we tried to get at least 10 patients with a 70 percent cure rate. But I would like to hear a specific answer for what the FDA accepts now.

DR. POWERS: I think there are two questions within your question. One is how many patients who are infected with a resistant isolate do you need? The second one, the broader question you asked, was how many do you need to study?

Let me answer the first one first. There are benchmarks for what we have done in the past. For instance, the database that levofloxacin had for penicillin-resistant organisms was about 15 isolates depending upon how you count it. But that is not an exceedingly large number for people with community-acquired pneumonia. When we asked this question of people in industry at the February, 2002 meeting, Dr. Goldberger asked Dr. Frank Tally how many isolates do you think we need and his answer was 15. So, it just happened to correlate with what we had looked at for penicillin-resistant Streptococcus pneumoniae and levofloxacin.

Now, the second question you asked was how many patients do they have to study to find those 15? But there is a hidden thing in that question

and that is who you choose to study. So, they had to study about 3000 patients to find those. There are two issues there. One is that levofloxacin was doing studies at a time when penicillin resistance was not as widespread as it is today. The second thing is that when you look at the original levofloxacin application and the licensing study for that, 57 percent of those people were outpatients who were not particularly ill.

So, if you choose to use a development program where you guide your treatments towards patients who are less likely to harbor resistant organisms, you are going to have to study a whole lot of people to find those cases. That is not up to us. What we have told sponsors is that if you want to look for resistant organisms you should probably gear your development program towards patients who are most likely to harbor those. We had this discussion again in July at an advisory committee about otitis media and about how to gear your development program towards patients who are most likely to harbor that.

We saw this development program in Augmentin where they had 50 isolates of penicillin-resistant Streptococcus pneumoniae in

kids with otitis media in one respiratory season because they gauged their development program towards the kids who were most likely to harbor those organisms.

DR. GOLDBERGER: If I could follow-up also on that, I think the other component in terms of thinking about the numbers, and again, I think levofloxacin is an example of this as is moxifloxacin, is collecting information about the effectiveness of the drug in penicillin, for instance, susceptible pneumococci since penicillin-resistant fluoroquinolones is clearly very much "out of class."

Again, we were very comfortable with, as John describes, what I think is a very reasonable and certainly a low number of cases of PRSP in fluoroquinolones because of buttressing our understanding of how fluoroquinolones perform in pneumococcal infections, using levofloxacin as an example, was about 250 patients with pneumococcal infection, including 55 patients with pneumococcal bacteremia which is considered to be a severe manifestation, that is, pneumococcal bacteremia and pneumonia with an overall cure rate of 100 percent.

So, that information as to how a drug

performs overall, including susceptible isolates plus some additional data, a relatively modest amount of additional data in resistant isolates to just tell us that if the patients who harbor resistant isolates are in some way different and the drug still works formed a very nice package. And, the model that we have used for levofloxacin we think is a useful way to proceed in developing drugs for "out of class" resistance claims. That is the model today and we have articulated these similar thoughts at meetings like this, as well as meetings directly one-on-one with sponsors.

DR. LEGGETT: Thank you. We will now take a break for eight to ten minutes max. Thank you.

[Brief recess]

DR. LEGGETT: We would like to get started now on the sponsor presentation. What we will do is try to stay on time so there will be plenty of time for questions. I am going to ask the speakers to go one after the other and for the panel and committee members to save questions until the very end of the sponsor's presentation, and we will try to do likewise for the FDA presentation and then reconcile any questions that still may linger at the very end before going to lunch and giving the

sponsor some time to bring back answers, or the FDA to bring back answers, if they cannot be answered before lunch, during that open public hearing if time remains.

I would like to introduce Dr. Gary Patou, the president of GeneSoft Pharmaceuticals.

Sponsor Presentation

Introduction

DR. PATOU: Good morning, members of the advisory committee and the FDA.

[Slide]

Ladies and gentlemen, I am Gary Patou, president of GeneSoft Pharmaceuticals. I led the development of gemifloxacin through its Phase I through III clinical trials, and I will lead you through the presentations today on gemifloxacin.

Many of you have been involved in the approval process for other fluoroquinolones and, considering this, I think you will appreciate me getting straight to the point. We believe there are two primary issues on the table here today. The first is why do we need another respiratory fluoroquinolone? Well, we are going to show you that gemifloxacin is not just another fluoroquinolone. It is uniquely potent and this

translates into clear clinical and microbiological benefits.

The second issue is the high incidence of rash that we saw in the clinical trials. Who gets the rash? When do they get it? How long does it last? But, most importantly, is it serious?

To answer these questions we conducted a Phase I volunteer study in 1000 subjects. This was a study agreed upon with the FDA. The rash was evaluated by a team of dermatologists, dermatopathologists and clinical pharmacologists. Many of them are here today to help address any questions the advisory committee may have. A substantial part of our presentation today will be addressing and asking questions of that particular study.

[Slide]

That is by way of introduction. Let me summarize gemifloxacin for you. The chemical structure of gemifloxacin is shown below. It is a member of the fluoroquinolone class. It is the most potent gram positive fluoroquinolone, with an MIC-90 against Streptococcus pneumoniae or 0.03. It is dual-targeting in patients and unique amongst the fluoroquinolones in being active against the

majority of Strep. pneumoniae organisms that are resistant to other fluoroquinolones.

[Slide]

Turning now to the pharmacokinetics, gemifloxacin is rapidly absorbed. Oral bioavailability is high, on average 70 percent. It has a long half-life, allowing for once daily dosing, and it is 55-65 percent protein bound with a large volume of distribution. Greater than 70 percent of the drug in plasma, urine and feces is unchanged gemifloxacin. So, metabolism plays only a minor part in the elimination of the drug. There are no significant drug-drug interactions with gemifloxacin since it is neither metabolized by nor an inhibitor of the cytochrome p450 system which is the major system for drug elimination in the body. Consequently, it has predictable pharmacokinetics. The drug is eliminated by both the renal and the hepatic routes with 20-40 percent of the drug going out through the kidney, the rest through feces. This means no dosage adjustment is necessary in any severity of hepatic deficit and only in the most severe instances of renal impairment.

[Slide]

The original NDA was filed by GSK in 1999

for a broad range of indications. A non-approvable letter was issued in December of 2000 and additional studies were conducted to address the issues that had been raised in that letter. This included study 344, a 1000 volunteer Phase I study designed in cooperation with the FDA. The NDA was resubmitted in October of 2002 by a new sponsor, LG Life Sciences, in collaboration with GeneSoft Pharmaceuticals and Parexel International acting as LG's U.S. agent.

LG Life Sciences discovered gemifloxacin and is Korea's largest R&D-based healthcare company. GeneSoft is an emerging pharmaceutical company also dedicated to anti-infectives.

The two indications that we are now seeking, acute exacerbations of chronic bronchitis, AECB, and community-acquired pneumonia, CAP, are those where the greatest unmet medical need exists and which we believe gemifloxacin can help address.

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To date, gemifloxacin has been assessed in nearly 10,000 subjects and just under 7000 subjects at the proposed therapeutic dose.

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We are seeking approval for a 320 mg dose

of gemifloxacin given once daily orally for 5 days for AECB and 7 days for CAP, all severities of disease. Please remember these short durations when we review the data on prognostic factors for rash.

We will also show you two types of efficacy data during the course of our presentations. The first are primary endpoints of clinical trials. We will also show you prospectively defined secondary endpoints that were agreed upon with the FDA during the protocol development. Examples of these secondary endpoints include bacterial eradication and duration of hospitalization in AECB. It is really important for me to point out that we are not seeking indication claims based upon secondary endpoints, but we do think that it is important to share these data with you as you consider the attributes of gemifloxacin.

[Slide]

Here you see our agenda and additional speakers for today's presentation. Dr. Low is Chief of Microbiology at Mount Sinai Hospital and professor of medicine at the University of Toronto. Dr. Low has published widely on Strep. pneumoniae

drug resistance and is on the NCCLS committee that determines antibiotic breakpoints for the United States.

Dr. Mandell is Chairman of the joint IDSA American Thoracic Society Treatment Guidelines Committee which recommends standard of care for community-acquired pneumonia in the United States.

Dr. Shear is professor of dermatology at the University of Toronto where he runs a clinic for patients with cutaneous drug reactions. Dr. Shear is at the forefront of research in the cutaneous effects of drugs.

[Slide]

As you can see on this screen, we also have a multi-disciplinary team of experts to answer questions in other ares of interest to the advisory committee. These specialists are drawn from dermatology, dermatopathology, immunology, hepatology, cardiology, pharmacokinetics and toxicology.

With that, I will turn the podium over to Dr. Low.

Unmet Medical Need

DR. LOW: Thank you.

[Slide]

Thanks very much, Gary. Let me just say that it is a privilege to be able to present before this committee. I see the task that I have at hand is to convince you of three things.

One, that emerging fluoroquinolone resistance is a serious concern, an issue. Two, one of the solutions to that problem is to use the most potent fluoroquinolone and the most potent fluoroquinolone, I believe, is gemifloxacin.

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Gemifloxacin is a functionally dual-targeting quinolone. Not that other quinolones aren't dual-targeting but gemifloxacin is the most potent dual-targeting fluoroquinolone, and I will explain a bit what that means in a few moments. It has unique activities against Streptococcus pneumoniae as evidenced by its PK/PD parameters, parameters which correlate with clinical efficacy and, not surprisingly, it has excellent activity against the other respiratory pathogens.

[Slide]

Briefly, let me define the problem of pneumococcal resistance or multi-drug resistant pneumococci. I think, first of all, we recognize

that the pneumococcus is the most common and important cause of respiratory tract infections, including pneumonia; that it is the one associated with the greatest morbidity and mortality and, if not treated appropriately, the one that is most likely to be associated with clinical failures.

I think what we have heard this morning is that over the last decade we have seen the emergence of antimicrobial resistance to the commonly used antimicrobials, including the beta-lactams, macrolides, tetracyclines and sulfamethoxazole.

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So, it has been a challenge to both academia and industry to come up with solutions to this problem. One of them is the development of new antimicrobials. One solution has been the development of fluoroquinolones, such as levofloxacin, that have enhanced gram positive activity against Streptococcus pneumoniae while retaining superb activity against H. influenzae and the other respiratory pathogens. Unfortunately, what we are seeing is the emergence of fluoroquinolone resistance in pneumococci.

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The next four slides are important to understand why this problem is emerging. The first slide shows you the problem of pen resistance in pneumococci. It took 50 years to get to the rates of resistance that we see today. In the 1980s we saw a low-level resistance, that we didn't pay much attention to, appear and emerge. In the 1990s we saw a high-level resistance emerge, as shown here in the yellow bars, and this high-level resistance is more likely to be associated with clinical failures. Obviously, that is why we are concerned.

[Slide]

On this slide you see a similar pattern with macrolide resistance. Macrolides were introduced in the 1950s. It wasn't until 15 years later that we saw the first macrolide-resistant pneumococci. It wasn't until the 1990s that we saw the worldwide dissemination of macrolide resistance in pneumococci. In fact, it has only been in the last year that we have seen peer reviewed published reports that have documented clinical failures that occur in patients who are infected with macrolide-resistant pneumococci and treated with macrolides.

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As you can see here, this is not true for pneumococcal resistance in the fluoroquinolones. Remember that ciprofloxacin was introduced in 1987 for indications which included pneumococci, and they are still in the package insert, but within four years we saw high-level resistance and, more importantly, we saw clinical failures. I am sure most of us remember that letter to the editor in The New England Journal of Medicine which described about 8 cases of pneumococcal pneumonia or infections that failed ciprofloxacin therapy.

[Slide]

So, why this discrepancy? I think you can understand it if you understand what the mechanisms of resistance are, how bacteria become resistant. The way the macrolides and the way the beta-lactams become resistant. The way the pneumococci become resistant to these classes is that they have to acquire complex pieces of DNA from other bacteria, thousands of kilobytes. Whereas, with fluoroquinolone resistance all it can take is a point mutation in one nucleotide to reduce the susceptibility of a pneumococci to one of the fluoroquinolones. So, there is a completely different mechanism of resistance and I think this

explains why we have seen the rapid emergence of fluoroquinolone resistance despite the fact that these drugs have only recently been introduced.

[Slide]

This is the disturbing slide. This is data from Hong Kong. Philip Ho and his colleagues have been doing surveillance. They showed, in 1995, that levofloxacin--MICs of 8 or greater--levofloxacin resistance was less than 2 percent, rates that we see currently in North America, but within 5 years rates of resistance increased to greater than 13 percent, that is by the year 2000.

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This is data from a recent U.S. surveillance program that was presented at ICAAC this year. I think this is the opportunity. Although the rates are still only 0.8 percent overall to levofloxacin in the United States, there are variations from 0-5 percent rates of resistance in some states and 0-22 percent in some cities.

What concerns me is that this is the pattern similar to what we saw with pneumococcal resistance to penicillin in the 1980s. That is, overall low rates of resistance with pockets of

high prevalence of resistance such as occurred in Tennessee and Kentucky, and were published in MMWR in the early 1990s. My concern is that we can see the very same rates for fluoroquinolone resistance if we don't do something with this window of opportunity that we have.

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What does it mean clinically? I think that we all appreciate that there has been a debate about the relevance of beta-lactam or macrolide resistance in pneumococci and what it means clinically is a difficulty in showing that resistance correlates with clinical failures. Let me say that this is not the case with the fluoroquinolones. Within only a few years of fluoroquinolone use for the treatment of pneumococcal infections, especially pneumonia where you have big burdens of infections, large numbers of organisms, we have already seen a number of clinical failures associated with resistance. In fact, there are over 25 reports either in abstract form or published form of levofloxacin failures.

[Slide]

In the past three years we have seen five published reports that have described 8 patients

that had pneumococcal infections treated with levofloxacin that failed therapy. Three of these patients died. I will show you data that explains not only why this happened but why it will continue to happen unless we adopt a new strategy for the treatment of pneumococcal infections with the fluoroquinolones.

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To explain why clinical failures have resulted and a solution to this problem it is essential that you understand how fluoroquinolones work and how resistance develops. Fluoroquinolones kill bacteria, and they do this very well. They kill bacteria by targeting enzymes that are essential for DNA replication. There are two targets within the bacteria that the fluoroquinolones bind to, ParC and GyrA, and resistance develops as a result of a spontaneous point mutation in either ParC, GyrA or both of these targets. In fact, all clinical isolates that have been reported to date from patients that have failed clinically or developed resistance on therapy with fluoroquinolones have had mutations in both of these targets.

[Slide]

Let me show you an example of resistance in an isolate of pneumococci and, at the same time, demonstrate to you the uniqueness of gemifloxacin in the face of emerging resistance. This is a strain of pneumococci that has an MIC to levofloxacin, this is an exceptionally low MIC to levofloxacin of 0.038, and a typical MIC to gemifloxacin of 0.016. If there is a mutation in ParC you can see a 32-fold increase in MIC to levofloxacin as compared to only a 4-fold increase in MIC to gemifloxacin. A mutation in ParC results in a 20-fold increase in MIC to levofloxacin but only a 1.4-fold increase in MIC to gemifloxacin. If you have mutations in both ParC and GyrA you can see that the levofloxacin MIC increases by greater than 1000-fold, but only by 64-fold to gemifloxacin.

I think the key point here to take away is that the MIC is still only 0.25, and after you, guys, get over arguing about breakpoints, this is not resistant; 0.25 will not be resistant and I think that is a unique characteristic of gemifloxacin.

[Slide]

So, why is it important then to have a

dual-targeting fluoroquinolone? Why is it important to have a fluoroquinolone at therapeutic doses that is able to bind to both targets and to inhibit and kill the bacteria? It is important because these mutations are being found in the lungs of patients with pneumococcal pneumonia when they first present to the doctor's office or the emergency department with pneumococcal pneumonia.

Why is that? Well, you can calculate it. We know from numerous publications that the frequency of first step mutations is about 1 in 10^7. We also know that the second step mutations actually occur more frequently about 1 in 10^5. We know that patients with pneumococcal pneumonia--and these are studies done in the '40s where they literally took lungs and did colony counts on those patients that died of pneumococcal pneumonia--have about 10^{12} to 10^{14} bacteria in that lung. Therefore, it is not surprising that we see in somebody with pneumococcal pneumonia, prior to the onset of therapy, that about 10^5 to 10^7 isolates will have a first step mutation and up to 100 isolates will have a first and second step mutation.

You could argue, well, that is crazy because every patient then would fail therapy if

you used a drug like ciprofloxasin. Well, there are many reasons why a patient responds to treatment and gets over pneumonia. One of those is host defenses. Another is the activity of the drug and is the drug getting to the site of infection. But this helps explain, helps us understand why failures have occurred and resistance has developed in a period as short as over 3 days.

[Slide]

The problem of emerging resistance of fluoroquinolones is analogous to a problem that we saw several decades ago, and we addressed that problem by using drugs appropriately. That is, emerging resistance to anti-tuberculosis drugs.

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Like some of the fluoroquinolones currently on the market, anti-TB drugs were only effective against one target in the bacteria. Just as the fluoroquinolones though, resistance was the result of the de novo spontaneous point mutations in the drug target.

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I think what I would like to get into now is to present you data on how does it differentiate from moxifloxacin and the other fluoroquinolones.

This slide shows you the results of in vitro experiments where a pneumococcal isolate was exposed to sub-inhibitory concentrations of trovafloxacin, ciprofloxacin and gemifloxacin.

As you can see, despite daily passages up to 15 days, the gemifloxacin MIC only increased by 32-fold as compared to greater than 100-fold for ciprofloxacin and greater than 500-fold increase in MIC for trovafloxacin.

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More importantly, if we look at clinical isolates and compare gemifloxacin's activity with the activity of currently available fluoroquinolones you can this collection of isolates. These are clinical isolates from patients where they have reduced susceptibility to the fluoroquinolones. In fact, they have mutations in both ParC and GyrA. On the far right-hand side you can see that gemifloxacin clearly has the most active in vitro activity against these non-susceptible strains, with an MIC-90 of 0.25. That I think is not resistant compared to an MIC-90 of moxifloxacin of 4 which is resistant; gatifloxacin of 8 and levofloxacin of 16. That is a 4-fold lower MIC for gemifloxacin.

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I think another characteristic of gemifloxacin is its unique activity that is not only reflective of low MICs but ability to kill organisms. This is an in vitro synergy time-kill experiment. What you see here is the ability of gemifloxacin, in the yellow line, to not only rapidly be bacteriocidal against pneumococci that are non-susceptible-- and I would point out that this is free drug concentrations that were used to simulate these experiments--it was not only rapidly bacteriocidal but, in fact, at 24 hours it was the only fluoroquinolone that was bacteriocidal with a greater than a 3-log reduction.

[Slide]

So, not only in vitro but in vivo gemifloxacin has better activity than the other fluoroquinolones, including moxifloxacin. Remember that the first-step mutants are essential to kill those first-step mutants if we are not going to have resistance emerge. You can see here in an animal model that gemifloxacin was statistically better than both gatifloxacin and moxifloxacin in reduction in pneumococcal log count and statistically better against gatifloxacin in

strains causing the infection that had two mutations.

[Slide]

Let me show you activity of gemifloxacin against clinical isolates that were not selected for resistance to show you its activity. Again, you can see exceptional activity of gemifloxacin with MICs of 0.032, 4-fold better than moxifloxacin at 0.25 and gatifloxacin.

[Slide]

When we look at the other respiratory pathogens, gemifloxacin does not lose any of its activity. It is either equal to the other fluoroquinolones or it actually has better activity than the other fluoroquinolones.

[Slide]

As you know, an important consideration today is another parameter, and that is PK/PD parameters. This is a concentration dependent killing that we are seeing here so it is important to remember that. One of the values that we use is the maximum serum concentration of the drug, that is, the C-max divided by the MIC. The optimal C-max to MIC ratio is 1 that has been calculated to be greater than 10.

Another measurement of activity is AUC to MIC ratios, that is, area under the concentration curve, and here the target for gram negatives is greater than 100 for H. flu. and E. coli but for gram positives the target is greater than 25.

I think another point to remember about pharmacokinetics here is that more is better than less. That is, maybe with time-dependent killing it is not so important but here more is better than less.

[Slide]

So, what is the evidence that these optimal PK/PD parameters actually make any difference in preventing the emergence of resistance? In fact, I think we have excellent data already available that these things work and we have examples where they don't work.

Here I think is an important example where the use of ciprofloxacin for the treatment of H. influenzae and M. catarrhalis in patients with acute exacerbation of chronic bronchitis, despite 10 years of the use of ciprofloxacin and other fluoroquinolones for this indication, resistance is almost unheard of. I think the reason for that is the exceptional AUC to MIC parameters and C-max to

MIC ratio that we have not seen resistance emerge in H. flu. and M. catarrhalis.

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If you look at gemifloxacin and its activity against pneumococci, you can see it has similar exceptional parameters with AUC to MIC ratios from 97 to 127. Remember, this is free drug to calculate these ratios, and remember there is more than one parameter when we are looking at PK/PD parameters. AUC to MIC ratio of greater than 10, that is, a ratio from 19 to 24.

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In fact, when we compare gemifloxacin PK/PD parameters with the other fluoroquinolones it clearly comes out on top. Yes, it is similar to moxifloxacin when we look at free drug but it clearly has better C-max to MIC ratios. Some would argue that this is a better predictor. In Preston's and Drusano's paper in JAMA, looking at levofloxacin therapy of community-acquired pneumonia C-max to MIC ratio was as important as AUC to MIC ratio, if not better.

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Probably more importantly though, what does this mean clinically? Might it have made any

difference for those patients who failed therapy with levofloxacin? In fact, we have been able to glean from the literature the susceptibility data on 8 patients who failed levofloxacin therapy. All isolates at baseline were susceptible to gemifloxacin. Five out of the 8 patients' isolates remained susceptible to gemifloxacin while becoming non-susceptible to levofloxacin, gatifloxacin or moxifloxacin. Finally, we found that an isolate from one of the patients that died remained susceptible to gemifloxacin.

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In summary, gemifloxacin has demonstrated excellent in vitro activity and maintains this activity in vivo. So, the question is, is it any better than moxifloxacin? I think that it is better than moxifloxacin. I think its in vitro activity clearly shows that against non-susceptible strains as well as susceptible strains it has 4-8-fold more activity. It has bacteriocidal activity that is better than moxifloxacin both in vitro with time-kill studies and in the in vivo animal model. Although its AUC to MIC ratios are similar, it has superior C-max to MIC ratios.

[Slide]

Thanks for your attention. I would like to introduce Lionel Mandell, who will talk about clinical efficacy.

Efficacy

DR. MANDELL: Good morning. I am Lionel Mandell, and it is a pleasure and an honor for me to address this committee.

You have just heard from Dr. Low about gemifloxacin's excellent activity against resistant pathogens in vitro. Let's now move into the realm of clinical medicine.

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Infectious diseases differ from all other medical specialties since the implications of treatment go far beyond the individual patient. With other medical specialties, such as cardiology or neurology for example, if an inappropriate drug is given the issue ends with that patient. With infectious diseases, however, an incorrect choice of antibiotics can lead to resistance problems which then affect many patients. So, with infectious diseases, when prescribing an antibiotic, ideally the physician must consider not only the patient at hand but society as well. Some drugs, like gemifloxacin, allow us to do both.

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I will begin by talking about the impact of AECB and CAP. Then I will describe the challenges we face today in the treatment of these conditions, and then for each condition I will pose two questions. One, has clinical effectiveness been demonstrated? Two, are there unique or differential features that the drug has shown for that indication? Then I will review the data that answer both these questions.

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Now let's look at the impact of both AECB and CAP. At any given time there are at least 13 million cases of AECB in the United States. Haemophilus influenzae and Streptococcus pneumoniae are major pathogens and emerging resistance is a major issue. The mortality rate in hospitalized AECB patients can be as high as 30 percent.

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As for CAP, there are 3 to 4 million cases of CAP in the United States annually and the impact of this is tremendous. There are at least 600,000 hospitalizations yearly, 64 million days of restricted activity and over 64,000 deaths. In fact, pneumonia is the seventh leading cause of

death overall and the number one cause of death from infection.

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As I mentioned a few moments ago, one of the biggest challenges we face in treating AECB and CAP is resistance to commonly used antimicrobials including some of the newer fluoroquinolones. As Dr. Low described, we are beginning to see treatment failures and even deaths on fluoroquinolone therapy.

We are also concerned about the enormous growth in the population of patients most vulnerable to AECB and CAP, namely the elderly. Incidence and severity of disease, as well as antibiotic resistance, all correlate with increasing age. The elderly often have comorbidity that requires additional medications and maintaining mobility of those patients and reducing hospitalization is particularly important in that vulnerable age group.

[Slide]

Please keep these challenges in mind as I review the data on gemifloxacin, beginning first with AECB. Let me remind you also that standard antibacterial clinical studies are sized for

non-inferiority to the comparator. But even in this context gemifloxacin demonstrates differentiable benefits, as I will show you.

[Slide]

So, 1267 patients received 5 days of gemifloxacin in 5 main AECB clinical trials. All were randomized, controlled trials and the first four were double-blind, while study 207 was an open-label trial. All the studies were non-inferiority trials. The primary outcome measure was per protocol clinical success at follow-up but I will also be showing you intention-to-treat data.

Gemifloxacin was studied against three well established comparators in three major antibiotic classes, the beta-lactams, the macrolides and the fluoroquinolones. Most patients had severity equivalent to Antonison Class I disease which has been demonstrated to benefit from antibiotics.

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This graph shows the estimated treatment difference with 95 confidence intervals for clinical success in both the per protocol and intention-to-treat populations for the three

principal clinical trials. Here we can see that in each trial the treatment difference was no less than the predefined non-inferiority limit. In all cases the confidence limit included zero. Results across these studies provide consistent evidence that 5 days of gemifloxacin is as effective as 7 days of comparator whether that comparator was a beta-lactam, a macrolide or another quinolone.

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The analysis of the bacteriological response at follow-up supported the clinical results just shown on the previous slide.

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In summary, three out of three principal studies meet the non-inferiority criteria demonstrating the effectiveness of gemifloxacin in AECB. In addition, the secondary endpoint of bacteriologic success shows high rates for gemifloxacin across all three studies. In each of these studies gemifloxacin was shown to be as effective when given for 5 days as the comparator given for 7 days.

[Slide]

Having shown you that the drug is effective in AECB, let me now show you

gemifloxacin's attributes in the AECB clinical trial program.

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Gemifloxacin results in faster bacterial eradication than does clarithromycin. Significantly more gemifloxacin-treated patients remained relapse free and fewer were hospitalized than with clarithromycin. When gemifloxacin was compared with an IV/oral cephalosporin switch regimen, it was statistically better in terms of clinical response for the intention-to-treat population, and subjects had statistically significantly shorter hospital stays in the analysis of the intention-to-treat population.

Also, in a head-to-head trial against a highly potent fluoroquinolone, trovafloxacin, gemifloxacin was statistically significantly better than trovafloxacin in terms of clinical response for the intention-to-treat population.

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In study 068 we see gemifloxacin's rapid eradication of Haemophilus influenzae compared with clarithromycin. Gemifloxacin eradicated Haemophilus influenzae in 100 percent of those cultured by the first day of treatment, while

clarithromycin still hadn't demonstrated complete eradication of H. flu. by day 6. This rapid eradication is particularly important since longer regimens generally promote antimicrobial resistance.

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Generally the major endpoint we look at in antibiotic trials is 2 weeks after completion of therapy. However, we wanted to see if gemifloxacin provided a longer-term outcome benefit. Study 139 was a 6-month follow-on to study 068. The prospectively defined primary endpoint was the proportion of patients in the intention-to-treat population who remained relapse free at 26 weeks. Employing the Bonferroni correction for multiple visits, the relapse rate was statistically significantly better in favor of gemifloxacin, with a p value of 0.048. The study also found a trend toward fewer hospitalizations with gemifloxacin, only 2.3 percent compared with 6.3 percent with clarithromycin.

Two related studies, however, failed to replicate these effects. Study 112 measured time to relapse as opposed to the relapse rate but relapse rates in both treatment groups were low

probably because the study was run during the summer months. Study 105 had baseline imbalances between the two groups. Twice as many patients in the gemifloxacin arm were on steroids, suggesting more severe disease in this group.

[Slide]

Study 207 is one of the supportive studies comparing 5 days of oral gemifloxacin with 10 days of IV/oral cephalosporin for patients requiring hospitalization. This graph shows the clinical and bacteriological success rates for both per protocol and intention-to-treat analyses. Gemifloxacin was as effective as cephalosporin in the per protocol populations, and in the intention-to-treat analytical was statistically superior for clinical success.

This is very important because keeping patients off IV can maintain mobility which is crucial in elderly patients. I will be going into more detail on this when I discuss the CAP studies.

[Slide]

Length of hospital stay was a prospectively defined secondary endpoint evaluating an important outcome measure. The percentage of patients discharged at follow-up was higher with

gemifloxacin although not statistically significant. The time to discharge, however, was significantly shorter for gemifloxacin, 9 days as opposed to 11 days for comparator and the result was statistical significant, with a p value of 0.04.

[Slide]

In study 069 5 days of gemifloxacin was compared to 5 days of a very potent quinolone, trovafloxacin. In the per protocol population gemifloxacin was found to be as effective as trovafloxacin. In the intention-to-treat population, however, gemifloxacin was significantly better than trovafloxacin for clinical success.

[Slide]

Turning now to the CAP indication, let's look at whether clinical effectiveness has been demonstrated.

[Slide]

The clinical program consisted of 4 randomized, controlled studies with non-inferiority design and two uncontrolled studies to help assess the efficacy of the 7-day regimen. Three of the 4 controlled trials were double-blind and one was open and 1349 patients received gemifloxacin at a

daily dose of 320 mg for 7-14 days. The primary outcome measure for 5 of the 6 trials was per protocol clinical success at follow-up. For study 287 the primary outcome was bacteriological response at follow-up.

[Slide]

Fifty-eight percent of study subjects were either ill enough to require hospitalization, were bacteremic or had severe CAP according to defined criteria. Again, no significant differences were noted between the regimens. A high proportion of the patients were elderly, assuring us that gemifloxacin was effectively assessed in this growing but very vulnerable population.

[Slide]

The primary endpoint for clinical studies was success at follow-up in the per protocol population. Also shown here is the pooled analysis across the studies. In study 012 the lower 95 confidence interval was minus 10.1 percent, which was only 0.1 percent outside the predefined delta. The confidence intervals for the intention-to-treat population are also lower, failing to indicate equivalence. Except for the one small difference in this study, all the study showed gemifloxacin to

be as effective as the comparators.

[Slide]

This graph shows how effective gemifloxacin is against the pooled comparators in all CAP studies for eradication of select bacterial and atypical pathogens.

[Slide]

In summary, three of the four principal studies meet the non-inferiority criteria for the primary endpoint.

[Slide]

Now I will address the question of whether gemifloxacin demonstrates differentiable features in the CAP program.

[Slide]

It is effective when given for 7 days of treatment in all severities of the disease, both in the hospital and out in the community. Oral gemifloxacin is as effective as an IV/oral cephalosporins switch regimen for hospitalized CAP patients. As in AECB, gemifloxacin again shows statistical superiority in the intention-to-treat analysis against trovafloxacin, another very potent quinolone. And, it is effective in eradicating pneumococci resistant to penicillins, macrolides,

cephalosporins and ciprofloxacin.

[Slide]

Analyzing data from all the CAP studies, we see that in trials specifically looking at 7 days treatment only gemifloxacin demonstrated high clinical response rates. It was as effective as the comparator in both the randomized, controlled trial and the 7-day data pooled from the 7-14 day clinical trials.

[Slide]

This is a similar analysis of patients with severe CAP according to the defined criteria. Gemifloxacin is as effective as comparators in both the 7-day fixed regimen and in the 7-14-day regimen. These data confirm other recent studies showing that severe pneumonia can be effectively treated with shorter regimens.

There is a growing body of data, recognized by the IDSA and the ATS Treatment Guidelines Committee, that even in infections as severe as ventilator-associated pneumonia the pathogens are eradicated and the parameters reflecting infection have resolved within the first several days of treatment, and adding a second week of treatment does nothing more even in these

severely ill patients with VAP than lead to colonization with resistant pathogens.

[Slide]

The shorter treatment regimen was also highly effective in hospitalized patients. More than three-quarters of the hospitalized patients in the gemifloxacin group received only 7 days of therapy. Although not shown here, gemifloxacin also appeared to be as effective as comparators for treating bacteremic patients.

[Slide]

Study 185 was specifically designed to compare oral gemifloxacin with IV/oral cephalosporin in hospitalized patients and 21 percent of these patients were defined as severe, defined as Class IV and V. Oral gemifloxacin was as effective statistically as its comparators for both clinical and bacteriological response.

This is very important because there is a very common misconception that we have to treat hospitalized patients with IV antibiotics. This simply is not true. One of the worst thing you can do to a patient who is fighting to avoid the use of a walker is bring him or her into hospital, hook them up to an IV and then make them a prisoner in

their own bed. After a week of being immobilized like this you can virtually guaranty that that older patient is going to need a walker and rehabilitation. There is a growing trend toward using oral agents to encourage and to maintain mobility.

Generally, I strongly recommend IV drugs only if the patient is vomiting, is being mechanically ventilated or is hemodynamically unstable, and these conditions exist in only a very small percentage of CAP patients.

[Slide]

As in AECB, gemifloxacin was assessed in a head-to-head trial against one of the most potent fluoroquinolone, trovafloxacin. Looking at the clinical and bacteriological responses for the per protocol and intention-to-treat post-approval study, we see that gemifloxacin was as effective as trovafloxacin in the per protocol population and, again, was statistically clinically superior to trovafloxacin in the intention-to-treat population.

[Slide]

Looking at all of the CAP clinical trials, we see that 7 days of treatment with gemifloxacin is also highly effective in eradicating

Streptococcus pneumoniae resistant to penicillins, macrolides and cephalosporins. In addition, there were patients with ciprofloxacin noon-susceptible isolates with MICs of 2 or 4. Gemifloxacin showed a high success rate against these organisms, as anticipated from Dr. Low's excellent discussion of gemifloxacin's potency and spectrum of activity.

[Slide]

In conclusion, we have a clear need for more potent, more effective drugs for both AECB and CAP. In AECB gemifloxacin has demonstrated clinical effectiveness and shows a number of very important attributes and outcome benefits. The drug is also clinically effective in CAP and oral gemifloxacin was comparable to an IV/oral switch regimen of a cephalosporin. I believe that oral therapy, given for shorter durations, will soon be standard treatment for most patients with CAP and AECB.

Finally but importantly, gemifloxacin shows effective activity against Streptococcus pneumoniae resistant to antibiotics, including the penicillins, the macrolides, the cephalosporins and ciprofloxacin. Gemifloxacin's efficacy and unique features that I have described make it extremely

valuable for the treatment of both AECB and CAP.

[Slide]

Now I would like to turn the podium back to Dr. Patou.

Safety

DR. PATOU: Thank you, Dr. Mandell. I will now being our presentation of the safety data.

[Slide]

I am going to tell you about the overall frequency of adverse events. Then I will show you the serious adverse events and withdrawals. Then we will walk you through gemifloxacin's safety record in terms of the key class effects of quinolones, including hepatic safety. Then Dr. Shear will address the data on cutaneous manifestations.

[Slide]

Shown here are the most frequently occurring adverse events reported on gemifloxacin treatment. Gemifloxacin is associated with a low incidence of adverse events, generally similar to or lower than the adverse event rates seen in comparators and of mild to moderate severity. The exception is rash. The frequency of rash was 3.6 percent versus 1.1 percent in the comparator group.

[Slide]

As you can see on this slide, the serious event rate, withdrawal rate and death rate with gemifloxacin is similar to the rates seen with the pooled comparator group. I have broken out for you the serious adverse events related to rash and Dr. Shear will review each one of these cases in turn with you during his presentation.

[Slide]

As a class, other quinolones have demonstrated specific side effects. Gemifloxacin was rationally designed to reduce or effectively eliminate some of those class effects, such as phototoxicity and CNS stimulation.

[Slide]

The only drug interactions observed with gemifloxacin were the class interactions observed with all fluoroquinolones, namely the ones associated with antacids and sucralfate. Gemifloxacin has low phototoxicity potential comparable to ciprofloxacin, and there is no dysregulation of glucose homeostasis as we have seen with other fluoroquinolones such as gatifloxacin.

[Slide]

QTc prolongation is another important class effect of fluoroquinolones and the patient study showed that gemifloxacin increased the QTc by a mean of 2.6 milliseconds. There were no reports of Torsade de pointes, the clinical consequence of very prolonged QTc. None of these cases were observed in gemifloxacin-treated patients. For comparison, we have included the data for other fluoroquinolones on this slide, taken either from the package insert or from publication.

Co-medications capable of prolonging QTc interval which compete for or inhibit cytochrome p450 are potentially an issue with this class of drugs. Gemifloxacin does not inhibit and is not cleared by the cytochrome p450 mechanism. Therefore, this type of drug-drug interaction is not of concern with gemifloxacin.

[Slide]

I will now discuss the drug's hepatic safety.

[Slide]

I am going to break the analysis into a number of parts. I am going to first look at patients who have a normal pretreatment alanine transaminase or ALT, which is a sensitive marker of

hepatocellular liver injury. I will then look at subjects who had an elevated ALT value pretreatment. That is, they had some underlying liver problem at least biochemically. Then I am going to review the incidence of hepatic adverse events in subjects with underlying liver disease, and the clinical trial database has been reviewed independently by Dr. Paul Watkins and Dr. Jim Lewis, both noted hepatologists. They are in the audience to take questions and my presentation is a consensus of both their reviews.

[Slide]

Shown on this slide is the incidence of ALT elevations on therapy for subjects receiving 320 mg of gemifloxacin. Moth stayed within normal range and comparable rates of elevation were observed with both gemifloxacin and pooled comparator. No patients on gemifloxacin therapy had elevations greater than 6 times the upper limit of normal.

[Slide]

We also looked at subjects receiving 640 mg of gemifloxacin, twice the proposed recommended dose. There is a slightly higher number of cases of ALT elevations in the gemifloxacin group

compared to comparator. One patient had an ALT elevation greater than 10 times the upper limit of normal, and there was a second patient that had an ALT elevation just under 8 times the upper limit of normal. In both cases the changes were rapidly reversible and the patients were asymptomatic.

[Slide]

We then went back and mined the database for any signals for potential serious hepatocellular injury, and we applied two criteria which are commonly considered predictive of severe drug-induced liver injury.

The first is so-called Hy's rule, described by Hy Zimmermann, and this is a distinctive pattern of LFT, liver function test, changes with both an elevated bilirubin of 3 mg/dl or greater and a very high ALT, generally considered to be greater than 20 times the upper limit of normal. Hy observed that 10 percent of subjects meeting these criteria either died or required liver transplantation.

The second criterion was to look at eosinophilia associated with any ALT elevation greater than 2 times the upper limit of normal as a marker for hypersensitivity reactions.

We also went back and searched the database again, using more stringent search criteria than Hy's rule implies, to screen for any other subjects that we thought merited further review by Drs. Watkins and Lewis.

[Slide]

There were no cases of patients meeting Hy's rule or demonstrating eosinophilia at either the 320 mg or 640 mg dose levels. Using the very conservative database search parameters, there were 2 cases with a bilirubin of greater than 1.5 mg/dl and with an ALT greater than 2 times the upper limit of normal. In both these cases the ALT was less than 3 times the upper limit of normal and both bilirubins were less than 2.

The cases were reviewed by hepatology experts. They noted that the serum alkaline phosphatase was also elevated and, therefore, the rising serum bilirubin was not the result of hepatocellular injury. Dr. Watkins and Dr. Lewis concluded that there were no liver signals with the 320 mg dose in patients with normal baseline liver chemistry.

[Slide]

We next looked at subjects with ALT

elevations at baseline. This table, which can be found in your FDA briefing book, shows the frequency of ALT abnormality on therapy with pretreatment abnormal ALT levels. The FDA noted that there appears to be a higher number of gemifloxacin-treated subjects with an ALT elevation above 2 times the upper limit of normal in these subjects. However, this table by itself is inconclusive because it only shows ALT levels at one moment in time. It doesn't show what the ALT levels were prior to treatment, nor does it measure whether they increased or decreased on therapy. In order to analyze whether gemifloxacin did, in fact, change the ALT levels of these patients we did a dynamic analysis.

[Slide]

We looked at the patients who had a greater than 2 times the upper limit of normal ALT at baseline and we followed the patients over time to see if their values increased, decreased or stayed the same. We compared their ALT values at the on-therapy visit with baseline and also at the end of therapy visit with baseline.

Importantly, 93 percent of patients at the on-therapy visit and 96 percent of patients at the

end of therapy visit showed either a decrease in ALT or no change in ALT. There were only 6 patients who showed an increase at either visit.

[Slide]

Let's take a closer look at those 6 patients. Shown here are the actual values for ALT and bilirubin. Bilirubin was normal pretreatment and did not rise in any patient. In fact, in 5 of the 6 patients the bilirubin actually fell. The highest ALT attained was 501 in the last listed patient, which represents a 5-fold increase from baseline and, in fact, was coming down again by the end of therapy. In the other subjects the ALT elevations were 3-fold or less. So, none of these patients came anywhere close to meeting Hy's rule and none of them showed any evidence of eosinophilia. The hepatologists did not find these liver function changes of concern.

[Slide]

We also looked at hepatic adverse events reported in subjects with underlying liver disease. All of these reports were descriptions of liver enzyme changes. There were no clinical findings, and none of these adverse events were reported as SAEs. Importantly, there were fewer subjects

withdrawn from the gemifloxacin-treated group related to these AEs than in the comparator group.

[Slide]

Serious adverse events related to the liver were reported in 4 gemifloxacin-treated subjects. All of them were from an unblinded study, study 185. All were reported as liver function test abnormalities. In fact, the ALT values were not more than 5 times the upper limit of normal in any of these cases. All of them were asymptomatic. There were no clinical reports associated with these biochemical changes. All have already been reviewed included in the biochemical analyses I have just described to you. Specifically, none of them met Hy's rule; none of them demonstrate any eosinophilia. We think that the investigators, knowing that the patients were receiving an investigational drug, were cautious and reported these as serious adverse events.

[Slide]

In summary, the hepatic profile of gemifloxacin at the recommended dose was devoid of any defined signals for serious hepatotoxicity potential. No subject met criteria for treatment emergent Hy's rule. There were no signals of acute

liver failure or irreversible liver injury or of hypersensitivity.

At the 640 mg dose there is a higher frequency of ALT increases, however, no subjects met Hy's rule and there were no signals for irreversible liver injury.

Finally, when we looked specifically at subjects with preexisting liver disease we found no evidence that these preexisting conditions represented a safety concern.

[Slide]

With that, I will turn the podium over to Dr. Shear for his analysis of the dermatological effects of gemifloxacin. Thank you.

Cutaneous Manifestations

DR. SHEAR: Good morning.

[Slide]

I am going to be reviewing the rash issue which is obviously of interest here, and I am going to be giving my presentation in three parts. First, Dr. Bigby presented very nicely "drug rash 100" and I guess what I am going to present is "drug rash 101" just to put this in perspective, with a few pictures and to make sure we are all talking about the same terms and it is not because

of your lack of knowledge in this area, I think it is because it is an area that has been very poorly defined over the years and we are just starting to get somewhere with it. This is the kind of approach that I used to teach other dermatologists about rashes, and I will be using that little yellow triangle in the corner to explain what I am talking about.

Secondly, I will show the study data from the clinical trials and tease out the rash issues that we see and look at the data there.

Then I am going to be presenting this very special study, 344, which looked at the rash in a most incredibly intense study ever done just for a drug rash.

[Slide]

I call this the rash diagnostic triangle. The fact is that we need to have an approach to drug rashes that goes beyond just looking and trying to describe what we see. When one looks at analyzing drug data you really need to look at each corner of this triangle.

First you need to look at the appearance, and I think this is something we see all the time but normally we just see descriptions of the

appearance. Some people use the term urticaria and different people might even disagree about what that is. So, even that is faulty and even with pictures you can try your best but that is not enough.

You also need to know if there is systemic involvement with the rash because that is going to change your assessment of what the rash means. Finally and ideally, you would like to have the histology of the rash.

None of these stands alone. I think if you only have one or two corners of the triangle you really can't make a full assessment. It doesn't mean you can't make one; it just means you have to realize you don't have everything you need.

[Slide]

This slide shows a variety of drug eruptions and basically are some pictures of what Dr. Bigby showed before. But the rash of interest here with gemifloxacin is this exanthem. This is an example using amoxicillin. As he showed, the aminopenicillins are the ones that most commonly have been reported to cause this in terms of incidence but also because these drugs are very commonly used. Probably overall they are the most

rashes that we see.

It is also important to note that this clinical appearance can be interpreted by different terms by different people. I think historically it was not as clear and most recently, in the data that Dr. Bigby showed, it is clear that we are starting to agree on at least some of the terms and descriptions.

[Slide]

In this next one, these are the terms that we use as exanthem, which is by no means an ideal term. Exanthem usually refers to an external manifestation of an infection, as most of you obviously know, but urticaria and other eruptions can do that as well so one could say they are potential exanthems.

The other term, maculopapular eruption--I certainly agree with Dr. Bigby, I don't like that term at all but it is a term used by many clinicians in many environments, and I am sure many of you here use that term. No offense, but we don't like it in dermatology but we don't have a better term. This is often just called drug rash and these are all called drug rash. Usually when I am finished with this part when I am giving a

lecture or teaching people, I usually say this may be something called "Shear" syndrome but right now it doesn't have a good name so it is wide open. If anybody wants to make a name for the most common drug rash and probably the most common side effect from drugs, especially antibiotics, it doesn't have a name and that makes it very difficult.

Down the line you have what is really a classic urticaria and I use urticaria because it is really descriptive. We don't know everything about this patient just by looking at the picture. I apologize because this is difficult to see but this is a patient who was on isoniazid for TB prophylaxis and she has about 30 pustules on each cheek, which are very uniform in the aciniform eruptions that you get fro isoniazid.

This is a patient who has a blister of a fixed drug eruption that Dr. Bigby mentioned. It is not always bullous but it can be blistering sometimes and this is from tetracycline and he has about 9 lesions on his body.

[Slide]

I mentioned that we look at the appearance and that is a beginning to the assessment. The second thing is to look at whether there is

systemic involvement. One of the key markers we have been impressed by in doing this work for the past 20 years is how important fever is. So, when we see fever we also look for systemic involvement. If we have an exanthem with fever and systemic involvement we are thinking about possible hypersensitivity syndrome. Usually, by definition at least in the studies we do and whenever we are reporting these, we are also looking for concomitant internal organ involvement. It doesn't have to be hepatitis but in the big series we did with dilantin, in the Journal of Clinical Investigation in 1988, about 50 percent of those patients had hepatitis but 25 percent can have nephritis and there can be other organs that are involved as well but less commonly.

An urticarial eruption with fever and arthralgia could represent serum sickness like reaction. It is not serum sickness. In fact, it is not even like serum sickness--another bad name. This is not an immune complex mediated disease but these patients will have fever, this sort of urticarial rash, and they have arthralgia and Cefaclor is a classic for that.

If one has generalized pustules with high

white count, this is emergent drug eruption which we probably years ago called pustular psoriasis by mistake but now understand it as AGEP or acute generalized exanthematous pustulosis, and that is not relevant to today's discussion.

Then, of course, there is the one that is very rare, as Dr. Bigby mentioned, Stevens-Johnson and TEN, and this is a spectrum of a blistering disease that is characterized clinically by mucosal involvement but that mucosal involvement is quite dramatic, and on the lips especially it is a hemorrhagic crusting that one sees on the lips and not just, you know, dryness or simple aphthae.

We can get into the mechanistic part later. Dr. Werner Pichler is here who has done the seminal work in this area, and to go from this rash way over here to Stevens-Johnson/TEN, as Dr. Bigby mentioned, is not the way we see it happening.

[Slide]

The other important reactions when looking through a database are what might be serious reactions or what might be signals of serious reactions. Obviously, angioedema, hypersensitivity syndrome and Stevens-Johnson/TEN are ones that we are looking for.

[Slide]

As a bit of background on the relationship between Stevens-Johnson and TEN, and this is perhaps my perspective on this but there are issues that make one think that hypersensitivity syndrome reactions might have some association and coexistence with Stevens-Johnson and TEN.

First of all, the pathogenesis is shared. There is a role of potential reactive metabolites, etc., and importantly, work that Dr. Pichler did showed that the T-cells that are infiltrating the skin--there is a strong presence of CD8 positive cells in the dermis, which was not the case for the gemifloxacin-associated rash but that is an important marker in both of these diseases and one that allows you to think that perhaps both occur through a similar pathway.

The reason that is important is when one looks at data like this hypersensitivity syndrome reaction for dilantin and Tegretol the reaction rate can be as high as 1/3000, and this is based on work that Rob Stern did, published in Neurology several years ago, using the Saskatchewan database. They didn't really have enough cases to get a strong assessment here but they were seeing rates

for dilantin and carbamazepine as high as 1/10,000.

This suggests that perhaps this hypersensitivity syndrome reaction could be a signal or a harbinger of cases in the future perhaps of Stevens-Johnson/TEN. That wasn't the case here but I just mention this because I think it is important in understanding what these rare signals can mean.

[Slide]

The other part of the triangle I talked about was the histology, and histology should not be the definitive answer. Even our pathologist, Dr. Wedad Hamma, who led the pathology group for the 344 study is here and she will admit that pathology is part of the clinical story. It is not the definitive part of the story.

Here is the histology of Stevens-Johnson/TEN and what one sees here is an attack of lymphocytes, especially CD8 positive cells, on the epidermis and hydropic changes. Over here, this is the epidermis but it is all pink which shows that it is necrotic. These CD8 cells are very good at elucidating things like fast ligands and other death signals to help kill the epidermis.

Again, that was not seen in this study but I think it is important to note that if a pathologist just saw this picture he might not be able to tell this from even a fixed drug eruption because they can show similar pathology. So, the pathology is just part of the triangle and part of the whole picture.

[Slide]

I have shown you the triangle. I think that is the best thing we can do and really we are very fortunate to have the 344 study to allows us to address each part of this, and we have to remember what that means but I am going to go to the clinical trial data first and just show you how we work with that.

[Slide]

There are about 10,000 people in all the studies but 6775 patients, as Gary said, received the drug at the therapeutic dose of 320 mg per day. It is important to remember that overall when one is looking at rashes, and these were exanthems, 4 percent roughly, or less than 4 percent, reported rash. So, we are looking at a prevalence of 3.6 percent. That is more than the comparators but overall. What Dr. Bigby showed you was for

aminopenicillins with rates of about 4-8 percent or 5-9 percent overall and this rate here was certainly below that. The median onset was 9 days and the mean duration was 5 days, which is actually the same finding as in the 344 study that I am going to show you so I think it just shows that this is a representative sample.

There were some withdrawals due to the drug and that was fewer than 1 percent of the patients because of rash and 1/1000 met the criteria for a serious adverse event and, as Gary said, I will go into those in detail.

[Slide]

There were 7 serious adverse events reported for rash in the 6775 patients. These 4 are clustered here for a reason. Each of these patients was hospitalized and that is why it was recorded as an SAE. All of these cases were from eastern Europe and I know from speaking with colleagues who do work in eastern Europe that the standard of admission is very different there. There is a much lower threshold for admitting patients. We don't even have dermatology beds in Canada. They have units with 55 beds in Prague for admitting patients and it is a whole different

approach.

When you go back and read these case reports there is nothing that is anything more than a benign rash with these cases, some itchiness, truncal erythema. There was no mucosal involvement; no systemic concerns; and this is clearly something that would be treated perhaps only with topical corticosteroids or oral antihistamines if it was, in fact, treated at all in North America.

[Slide]

In these three cases from western Europe and North America we have first the case from Canada. This patient was afebrile and it was called serious in a decision by the investigator. We are not really sure what that is based on but the rash cleared in 2 days. So, there was nothing impressive there.

The patient from the Netherlands was complex in that they were receiving 8 co-medications. The rash came up quickly, resolved by day 18 and all they were treated with was antihistamines, and they were not admitted to hospital.

The case from the United States perhaps

had more substance. This was reported as serum sickness but I think what the person was really trying to describe was a serum sickness like reaction. Serum sickness is different. It is from foreign proteins, an immune complex mediated disease, etc. but serum sickness like reaction is sort of what we saw here. This is a person who had rash, sore joints and fever. The odd thing was that it was about 13 days after the last dose of the drug, which is about 40 half-lives out, and usually, if we look at Ceclor as an example, it is about 5-10 days into therapy. But this might be a serum sickness like reaction.

In summary, we have 7 reported SAEs, one that may be a serum sickness like reaction. I also reviewed 6 cases of facial edema because that might make one think of angioedema and might make one think of hypersensitivity syndrome. In all 6 of those cases, and the FDA agrees in the case book, if I remember, this was not a marker of anything else. These patients had no systemic symptoms.

[Slide]

The other issue the FDA asked the sponsor to look at were important questions regarding re-exposure to quinolones. Basically, going over

that clinical trial database was one way to answer it. In patients who had a previous exposure to another quinolone and then got gemifloxacin, there were just over 180 people and 3 of them got minor rashes on gemifloxacin, which is a rate of less than 2 percent.

The previous exposure with gemifloxacin for those who had no rash but then got gemifloxacin again perhaps months later in another study, there were 41 people who fit that criteria and none of those people got a rash.

In subsequent exposure to another quinolone after a gemifloxacin rash, there were 11 people who gave a history of quinolone rash and then when they got gemifloxacin they had no adverse event in the skin.

So, the question was looked at in these three different ways and each time there was no evidence of any important cross-reactivity.

[Slide]

Multivariate analysis was done from this clinical trial database and the covariates that were associated with rash are shown here: female gender, age under 40, as was mentioned in the FDA introduction, and longer duration of therapy which

was also mentioned and shown in very nice graphic form. What one sees is around 10 and 14-day rates of about 6.4 percent and 7.4 percent. In addition, in women over 40 there was a slight increased risk in association with use of hormone replacement therapy.

[Slide]

Pulling out the main numbers here using logistic regression to identify the highest risk group, it defined a rash rate of 15.3 percent in women under 40 who took the drug for 10 days, which is longer than the 5-7 days being asked for today. In the comparator the rash rate was around 2 percent.

[Slide]

It was this higher number in this subset and under these conditions of 10 days of exposure that prompted the idea to perhaps look at this in more depth. So, study 344 was designed to determine the characteristics of the rash. What was this rash? To really ensure that there were enough rashes to study, and when you try to think about doing this prospectively--and this has never been done before to my knowledge, so it is unique opportunity to think about study design,

interpretation of data, implications for approval, etc.--so here we have a population that was defined that might give us a high enough rate of rash, especially if we look really hard.

This was healthy women under the age of 40 in a Phase I setting. They took it for 10 days, as I said longer than you would take it for AECB or CAP, and they also looked at cross-reactivity in a second phase. So, people who got a rash were exposed to ciprofloxacin as a quinolone.

Another part of this was to look at subclinical sensitization so if you got gemifloxacin once maybe you didn't get a rash, but what if you got it again? Finally, what about the relationship of drug and its major metabolite and acetyl gemifloxacin? Was there a relationship there?

Just the answer to the last one since I have too many slides anyway, just to tell you that there was no relationship between the plasma levels, the AUC or the N-acetyl transferase activity in patients who got rash and who didn't.

[Slide]

Here is part A of the study. We are trying to get more than 3.6 percent. So, what we

do is take this at risk group of females who are 18-40 years old, weight it 5:1 in favor of getting gemifloxacin and they take 320 mg for 10 days because we know we have a higher rash rate at 10 days, and then see who gets rash and see who doesn't get rash.

Now, in all there were 841 women who received gemifloxacin and 170 who received ciprofloxacin so there were over 1000 cases. That is very impressive for a rash study, I have to say.

[Slide]

This is part B of the study. What we are looking at here is the disposition of individuals to try and answer this question of sensitization. So, here we are seeing rash in part A and we are trying to characterize that rash. In part B we are not ignoring the people who get rashes but we just want to answer some of these questions about cross-sensitization.

So, if you got gemifloxacin and you got a rash, then in you would get in part B, after washout, ciprofloxacin or a placebo. If you didn't get a rash you could look at subclinical sensitization by looking at gemifloxacin or placebo. Sort of as a background, ciprofloxacin

rashes got placebo and ciprofloxacin who didn't get a rash the first time got ciprofloxacin again for sort of looking at this subclinical sensitization issue.

[Slide]

For further clinical assessment subjects were assessed by board certified dermatologist in 30 locations in 7 countries. Besides photographs and clinical assessments, the FDA had asked the sponsor to collect skin biopsies, which is a good thing because that is the third corner of my triangle.

Ultimately, 288 subjects had biopsies taken from their rash. These include samples from the rash site but they also include samples from normal skin where there did not appear to be a rash. It is really unusual to do that but I think the reason there is to sort of look for a subclinical rash. By the time you see a rash maybe you are seeing something that, sure, is clinical but maybe there is something subclinical going on, and that is very unusual. We are going to review some of the pathology but this was sort of looked at in every way in blood and urine sampling and cardiograms, of course, were followed.

[Slide]

The numbers were remarkable. I have said this before but basically all aspects of this were unique, even the idea of doing a study like this. But when it was done, it was certainly done right. There were samples taken for routine histology, immunofluorescence, immunophenotyping to take a look for those CD8 positive cells, looking at drug levels and metabolite levels, and ended up with 1000 subjects, 10,000 slides and 16,000 samples. At the end of this there was no association with the drug or metabolite levels and only minimal inflammation in the skin.

[Slide]

The study did pick up, as expected, a high number of rashes. Here you will see 260 patients of the 800 or so, almost 32 percent, got a rash. When one looks at that data in that subset you wonder what that means, but that is comparable, if you want to look back at what was seen in the clinical trial database, to 15.3 percent in the clinical trial database. The cipro. rash was also more common, about 4 percent, compared to the background of around 2 percent in the clinical trials. There is no doubt when you see the rashes

that ascertainment certainly plays a role. If you are going to look closely every day for 10 days you are going to see rashes that would often just be passed off as nothing. So, this is important.

[Slide]

Here is the timing. What one sees here is the day of onset. So, everybody gets 10 days of therapy. If they develop a rash the drug is stopped. Of the 100 percent of people who got rashes with gemifloxacin in part A, one can see that 42 percent of those occurred on day 9. Of those who got rashes, 82 percent of all the rashes occurred in these 3 days. Very few rashes before day 8 and very few rashes after the drug was stopped.

[Slide]

So, to start looking at the aspects of what this means in study 344 when you are looking beyond the numbers and starting to look at the cases and the case record forms for what was going on in the skin, we go back to this triangle idea. Here we are just going to look at the appearance.

This is sort of an average type of rash. Most people on this study who got a rash, this is the kind of rash they had, little, tiny red papules

scattered around. We are not going to show you the front and I am not going to show you the legs but pictures were taken all over.

As far as the worst goes, as bad as it is, there is no name for this disease. There is no definition of "worst" and what we have done is we have reviewed all these pictures and since most of them look like this it is not very interesting, but there are about 5 or 6 rashes that would be around this sort of severity. So, the idea is you can see that there is deeper erythema. It is coalescing in areas and it seems to have a break here, which might be the bra straps, and one sees in a few patients.

I just want to make a comment about that. Dr. Bigby mentioned sometimes pressure does induce rashes and sometimes I think it prevents rashes. People lying in bed in hospital often will get a rash on their back. I don't know if it is because of drug delivery, different heat, whatever, but in areas that have been under pressure, like belts, and bra straps, you often don't see as much of a rash and we will see that in a few people, but the pathology did not show any phototoxicity or changes associated with phototoxicity.

[Slide]

These are the severe cases. Seven percent of the rashes were coded as severe and the definition of severe was that it interfered with your daily activities. I just want to show you the appearance of the ones that we have photographs for, just so you get an idea, a bit of a gallery of what these look like because it is really hard to quantify these, and a picture is worth a thousand words and I want to spare you the seven thousand words or so.

[Slide]

Let's go on.

[Slide]

And again. You can see again this sort of appearance but really when you look at this closely you will see rash in there as well, it is just that the tanned area looks a little more impressive.

[Slide]

This is not a rash that a dermatologist would normally biopsy. I mean, it would only be a relative that would show you a rash like this, and if they did show you, you certainly wouldn't biopsy it and you probably wouldn't even treat it. Frankly, for some of these, even though these were

recorded as severe, any less rash than this would be no rash at all.

[Slide]

The other issue that came up were other morphologies that might be signals. Two that come up are the issue of facial swelling and the term urticaria and what does this mean. In this study the term urticaria was meant to be a clinical description with a view that some rashes would be urticarial. None of these rashes had the annular appearance of true urticaria and basically just showed this papular appearance a little more strikingly. In some of the photographs, because you get blanching around some of these, they look as if they stand out even more but that is more an optical illusion that one sees. You often see this whitening of the skin probably because of a prostaglandin effect surrounding the rash.

But the onset and duration of these so-called urticarias was the same as that seen with the typical exanthem. I am getting ahead with the histology but the histology is also similar to that seen with the typical exanthems. There was no swelling of the lips or tongue; no annular rashes on the skin; nothing that made it look truly

urticaria but just urticarial.

For the facial edema, this usually referred to the rash being on the face. We only have a few pictures of the face. It was not part of the study generally to take pictures. So, if anyone had anything severe that looked a little more red, that was taken and generally it wasn't urticaria and it wasn't generalized swelling; it was just the rash on the face that was swollen. So, that was reassuring. There was no true urticaria and nothing to support angioedema.

[Slide]

Continuing with the diagnostic triangle, we are also looking at the systemic appearance. I mentioned that mucosal changes could be important, and specifically we are interested in hemorrhagic crusting or more erosive changes and those were not seen. But there were changes like dryness of the lips and typical aphthae, and one person had macular erythema. Wheezing was seen in one patient but they had no signs of any type-1 or hypersensitivity reaction associated with that and it seems to be just an isolated finding.

Six patients who had fever with rash, in reviewing the CRFs there was nothing of concern

except there was one that had lymphadenopathy associated with this, and all we have in the check box is lymphadenopathy. The patient's rash cleared in a couple of days. They weren't admitted to hospital, and the histology did not show CD8 positive predominance like one sees with hypersensitivity syndrome, and they did not have any liver or urine changes that, again, would suggest systemic involvement. So, we were quite reassured in looking back on that one. The rash looked a little redder but the pathology was as benign as all the others. It cleared quickly and there was no systemic involvement so we don't think that is a true hypersensitivity syndrome.

[Slide]

Looking at liver enzymes, there were no clinically significant changes in this study; no differences in ALTs between women with rash and those who didn't have rash; and no changes in the eosinophilic count that were of importance.

[Slide]

Now the histology. This is the final part of the triangle. Assuming that you are not all horribly familiar with skin biopsies, let me just show you. This dark part, here, is the epidermis.

One of the things one would look for, of course, would be either changes at the interaction between the epidermis and the dermis, like one sees in Stevens-Johnson or other reactions, and, no, there aren't.

Is there necrosis or changes in the blood vessels, like vasculitis? No, there aren't. In fact, what you see here is lymphocytes which are predominantly CD4 positive, which is what one sees in the mildest of drug rashes. This is what was seen in 278 of the 288 biopsies--this picture, slightly more or slightly less over and over and over again.

This is sort of the worst one because the ones which were at the mild end, which is 80 percent of them, you can hardly even see the lymphocytes.

When you look at the 10 cases that had moderate superficial and deep lymphocytic infiltrate, again they were CD4 positive and, in reviewing these cases, there was nothing that was striking about them clinically.

In the skin that was normal that was biopsied there were no subclinical rash changes. There was no pathology in the normal skin.

[Slide]

The immunohistochemistry, as I said, showed that these were T-cells and they were CD3 positive. There was a mixed population, predominantly CD4 positive, which is what one sees in these mild exanthems. This is a reassuring sign. There was no hint of erythema multiforme, epidermal necrosis or vasculitis. This all fits with just a general mild drug rash.

[Slide]

Now part B, looking at the issue of sensitization potential, and this has taken a complicated study and made it even more complicated but what one looks at here is three groups. I am going to go through these individually to make it easier to follow.

This group is people who got a rash on gemifloxacin and then were exposed to ciprofloxacin or placebo. In about 10 percent of people, which is about 6 percent more than the placebo rate so about 6 percent, if you will, overall got a rash on ciprofloxacin. There was one site that was considered an outlier and I see the FDA has taken that site out of theirs. We took a more conservative approach of including it here, but if

you take that out one sees an increased attributable risk of about 4 percent.

I think this is remarkable. We have heard things about "in class" issues and from our drug safety clinic and others who do drug safety clinics we have heard that people will react to Pan G and not to Pan V, let alone react to amoxicillin and not react to penicillin, oxacillin or others. So, it is very, very specific to the drug and there are good immunological reasons for that. I think the reason we tend to think of a class effect is based on the premise that these drugs work through the same way but the reason they work through the same way is we only pick the drugs to develop that are going to work. So, if a quinolone doesn't block these enzymes that Dr. Low showed you, it is not going to go on to development. So at the end of the day they all look the same but they are not really all the same. The ones that are different have dropped out because of efficacy and we are left with a legacy that we think they are the same but they are not.

I think anybody who is afraid of this would be surprised to say that if you took all the people who got a rash and 4 weeks later gave them a

quinolone and 4 percent of them, if you will, had a rash above placebo you would be really surprised. That is a very low number and I think that is very useful, and no other drug has this data so that is also very useful.

[Slide]

Looking at people who maybe had subclinical sensitization--you got gemifloxacin once and you didn't get a rash, what if you got it again and there is no difference between placebo or not. So, if you got gem. and you are okay, you are okay.

[Slide]

This was to look at some of the background, and what is interesting here is people who got ciprofloxacin once and didn't get a rash but got ciprofloxacin again, about 5 percent of them, or 3.5 depending on the data you use, got a rash on ciprofloxacin. The background rate with gemifloxacin actually was lower for people who got it twice.

[Slide]

When we looked back on the rashes in part B, we also wanted to look at what these rashes were. You might say, well, the rate was low but

maybe these rashes were really scary. We didn't get a lot of them but maybe they were scary.

They were all less than 10 percent of the body surface area. I have to say that when you read these case record forms body surface area is overstated, which is a problem and it was a problem we faced when we did the big study that was in The New England Journal looking at TEN. We had to have pictures of bodies to show you because if you got a couple of dots all over the place people tend to overestimate that. But this did not have much of the body surface area. No reports of mucus membrane involvement; nothing suggestive of IgE-mediated reaction; no systemic involvement; no elevated liver enzymes; and the rash came on a little earlier but was benign. So, I think what we found in part B was just a lot of very bland eruptions.

[Slide]

To summarize study 344, this was a remarkable study and after 10-day exposure in a population that is known to have an increased risk of a rash, the rash that was seen was generally very bland. It was a classical exanthem that one sees. There was no evidence of hypersensitivity

syndrome; no markers of Stevens-Johnson toxic epidermal necrolysis.

[Slide]

In the clinical trials the rash rate was 3.6 percent overall. The rash was higher in younger women after 10 days. After 7 days it was 10 percent, as you saw, and about 2 percent at 5 days.

There was one case of serum sickness like reaction in the database of 6,775 people and exposures and no cases that really fit the definition of a clinically serious rash like Stevens-Johnson/TEN or hypersensitivity syndrome. Those were not seen.

[Slide]

In conclusion, the rash rate with gemifloxacin in the general population that is exposed for treatment is 3.6 percent and that is a rate consistent with that commonly seen with many antibiotics, as you heard earlier. It did occur with an increased frequency in a subset of people who are not really the target treatment population and when the drug was taken for longer than is being asked for.

Study 344 was the largest and most

comprehensive drug rash study that I have ever seen in 20 years in the business of looking at drug safety in skin. What was found was conclusively clinically and systemically and histologically to be a mild inflammatory exanthem. There were no cases in the 10,000 subjects in the overall database of hypersensitivity syndrome of Stevens-Johnson.

So, this is a rash that may occur more frequently than seen with the comparators in the clinical trials, but I am very reassured from the clinical trial database and especially from this 344 study that the safety questions have been investigated extensively and have been answered clearly. Thank you.

Risk-Benefit and Risk Management

DR. PATOU: Thank you, Dr. Shear.

To sum up, gemifloxacin has been extensively examined in studies involving nearly 10,000 patients. The data show no clinically significant liver or QTc problems. The rash rate in CAP and AECB is greater than that seen with comparator, however, there was no evidence of significant morbidity observed. There is a low rate of cross-sensitization and there is no

evidence for subclinical sensitization with gemifloxacin usage.

[Slide]

I will now describe the benefit-risk for gemifloxacin. Really no assessment of benefit-risk would be complete without first reviewing the limitations of current medical treatment for these conditions. Because of resistance to the older classes of antibiotics, physicians have become increasingly dependent on the newer fluoroquinolones. As we have heard, there is now increasing resistance to these quinolones also.

[Slide]

As shown on this slide, each of the fluoroquinolones currently on the market comes with its own set of problems. With gatifloxacin life-threatening hyperosmolar coma has been reported. Moxifloxacin carries a warning for QTc prolongation. As Dr. Low has published and described today, levofloxacin resistance, which is now emerging, has been associated with pneumococcal pneumonia treatment failure and even death. Thus, there is a critical need for additional treatment choices in AECB and CAP, and we believe gemifloxacin is well suited to meet that need.

[Slide]

Looking at the benefits of the drug, gemifloxacin is uniquely potent against respiratory pathogens and has favorable PK/PD correlates. We have demonstrated that this allows us to treat patients with shorter courses of therapy. This would likely lead to better patient compliance and, importantly, would expose the commensal bacterial flora to less resistance pressure.

The dual targeting of the drug and its potency means that it is active against antibiotic resistant respiratory pathogens, including fluoroquinolone resistant pathogens. As Dr. Powers mentioned in his talk earlier, by the time the organisms are resistant to levofloxacin there really are very few treatment choices available.

The spectrum of its activity means that the drug is likely to be effective in empiric treatment in the community, regardless of whether the infective respiratory pathogen is antibiotic resistant. We have also demonstrated that the benefits of this drug extend beyond the acute treatment period, manifested as reduced relapse rate and duration of hospitalization in AECB, fully recognizing that these are secondary endpoints in

those clinical studies.

[Slide]

Gemifloxacin's excellent oral bioavailability, coupled with its potency, means this drug can effectively be used when physicians may otherwise have used intravenous therapy to treat their patients. We have demonstrated that oral gemifloxacin is equivalent in effectiveness to IV comparator regimens and obviates the need to immobilize patients.

The lack of significant drug-drug interactions with gemifloxacin is important because many of the patients affected with these conditions are elderly and on co-medications which complicate the choice of antibiotic. No dose adjustments are required, except in severe renal impairment, with gemifloxacin.

[Slide]

On the risk side, gemifloxacin has a good adverse event profile and was well tolerated, as reflected in the low withdrawal rates from studies. There are few quinolone class effects. There is no hepatic safety signal and we see a shorter QTc prolongation than with other quinolones.

There was an overall rash rate of 3.6

percent and clearly higher in a susceptible subpopulation that we studied. However, it was not associated with significant morbidity and had low cross-sensitization potential and no subclinical sensitization potential. As you heard Dr. Shear say earlier, it is a clinically manageable, typically mild drug rash.

[Slide]

I want to say a few words about risk management. We have obviously thought a lot about risk management. We have a twofold risk management strategy. The first is managing risk and the second is anticipating the worst case scenario.

First, we know that most of the rashes occurred in women younger than 40. Our target label population is patients with CAP and AECB and these tend to be an older patient population. In study 344 the rash occurred when the women took the drug for extended periods, that is, more than the 5-7 days that we are intending in our treatment indications of CAP and AECB.

We will provide the drug only in a 5- or 7-day fixed dosage pack. This means that we believe physicians will be unlikely to prescribe more than the intended course. As we explained in

an appendix in our briefing book, we have analyzed the impact of a fixed dosage pack and we believe that this strategy would be effective.

However, even in the event that none of these procedures is followed, study 344 clearly demonstrates that this observed rash is benign and uneventful for those patients who might get it. You recall what Dr. Shear said, never before has he seen a study as thorough and exhaustive as study 344 and he found no evidence in the study that the observed rash was anything other than a mild, benign drug rash.

The adverse events noted on gemifloxacin will be fully described in the package insert to the drug. In addition, we will provide physician education and we have proposed to the FDA, and we have been in some discussions with Rob Stern and others who are experts in this area, the study design for a Phase IV study to study the safety of the drug in the marketplace.

[Slide]

We conclude that gemifloxacin in the treatment of AECB and CAP would be a valuable, indeed a critically needed addition to the physician's armamentarium in the treatment of these

diseases. I thank you for your attention.

Questions and Answers

DR. LEGGETT: Thank you. Are there any immediate questions over the next five minutes or so before we take a break, and then we will come back. First Dr. Maxwell and then Dr. Bigby.

DR. MAXWELL: I have three questions related to the same issue, and that is the issue of women and estrogens. Firstly, although the reports are that most of the women that were affected were under the age of 40, what I wanted to know is were there any older women that were on estrogen replacement therapy that developed the rash?

The second part to my question was on slide number 32 where there were some aphthous buccal ulcers noted. I wanted to know if there was any other mucosal involvement in any of the women, vaginal or anywhere else.

The last part of my question, Dr. Bigby stated that you could develop a rash up to several weeks after exposure to some drugs. I want to know if there were any of the patients developing a rash that received the drug for the 5- or 7-day period that developed this rash greater than 2 weeks after exposure to the drug.

DR. SHEAR: Can I have slide R36? Actually, we can probably show 35 as well.

[Slide]

As I mentioned verbally, there was an association with hormone replacement therapy that showed a higher risk. What we are looking at here is the odds ratios and the 95 percent confidence intervals. So, we are looking at hormone replacement therapy use. It was around two. So, there was an increased risk with hormone replacement therapy, not as high as with the other risk factors.

[Slide]

This is our contraceptive use, which I think is relevant to the question. Here there was no statistically significant association. It was slightly higher but the confidence intervals crossed 1 and so it was not considered that oral contraceptive use was relevant.

The question about mucosal involvement, there was one case report in 344 that mentioned labial involvement. Now, I don't know if that meant that it was on the lips, but the implication I think was that it may have been on the vulva but there was just some erythema and possible erosions

but nothing striking. At least, there were no details there that made us think it was anything severe. That was in a patient who had some other changes and I think that will be discussed later.

[Slide]

In study 344 we had the chance to follow people very carefully. This is a complicated slide so let me walk you through it. It is not something we see very commonly. This is from the clinical trial population because we know in 344 people didn't get the rash much after the 10 days. But if you look at the trial population, what we are doing here is this is the number of days after therapy was stopped. The yellow is the gemifloxacin and the blue is the comparator. What we have here is that this number represents, if you added up all these, 100 percent of people who got a rash after the drug was stopped. We know what the rash looks like, but if 100 percent of those people got a rash after the drug was stopped, about a third of them were on the first day after the drug was stopped and about a quarter of them were 2 days later. Then, there were a few cases that came up later but there were no late surprises later on.

DR. LEGGETT: Dr. Bigby?

DR. BIGBY: The duration of treatment for those patients in this slide is what?

DR. SHEAR: The duration of treatment is a mixed bag. It is primarily 5 and 7 days. There are some 10 and the odd 14 because 14 wasn't used much.

DR. LEGGETT: Dr. O'Fallon?

DR. O'FALLON: This is more of a comment. I thought the rash study was very impressive. I wish you had presented confidence interval estimators on a lot of those things because when you have done a really big study you can get a lot of mileage out of that.

DR. LEGGETT: Dr. Adkinson?

DR. ADKINSON: Dr. Shear, I certainly share your belief that the clinical significance of rash is perhaps inferred from evidence of systemic involvement in reaction. So, I would like to ask for a little further information about these 7 severe adverse reactions that were attributed to rash. You have told us I think that the histology and the pictures taken of those rashes were quite benign and unimpressive. But I wonder if you could say a little more about other systemic features that might have been present during those hospital

stays, particularly fever and eosinophilia.

DR. SHEAR: There are a couple of bits of data that are important. In the 7 SAEs that were reported from the clinical trial database, 6 of those had really no important signs of systemic involvement. As far as eosinophilia goes, I don't have that. We don't know about the eosinophilia in those. The rashes were very mild, lasted a couple of days and went away. There was nothing to suggest urticaria and nothing to suggest systemic involvement. Are those the ones you are talking about?

DR. ADKINSON: And also with regard to the 6 cases that had fever and rash in the 344 study. Can you say something about the time course and the persistence of fever in those cases? Was it an isolated fever spike? Did it correlate with the rash? Did it persist after the rash disappeared? I am particularly worried about this group because if I understand it correctly the 344 study was conducted in normal subjects. Right? So, there shouldn't be other common causes for fever.

DR. SHEAR: Well, I think there are certainly issues when you are looking at 1000 people. Some people are going to get a fever.

Having said that, fever was defined as a temperature above 37.5 so it was a pretty low threshold for diagnosing fever. The way it was scored was just on a check box so they checked off that that was the temperature. The drug was stopped if people had rash, and the rashes lasted maybe 5 days, just like the others. There was nothing different in terms of the duration. But the fever was hard to chart. In follow-up visits 2, 3 days later people were generally recovered.

DR. ADKINSON: And was eosinophilia looked for in these cases?

DR. SHEAR: No, eosinophilia was not part of that.

DR. ADKINSON: Was not part of that? So it was looked for and not found?

DR. SHEAR: It was looked for and not found.

DR. LEGGETT: Dr. Epps?

DR. EPPS: I just have a brief question at this point. What was your ethnic breakdown in study 344? The reason I ask is that a 2-5-day rash can sometimes result in months of hyperpigmentation or hypopigmentation, which is what ends up at the dermatologist's doorstep, and certainly something

that is benign from this aspect or your consideration may be prolonged and very distressing for a patient.

DR. SHEAR: My apologies, what was the very first part of the question?

DR. EPPS: The ethnic breakdown.

DR. SHEAR: In 344? I can get you some information but in the clinical trials there were rashes and the rate in people with white skin was 3.8 percent, which was similar to the overall. In the non-white skinned or darker skinned individuals, there were about 1000 people who were involved in the studies and the rash rates ranged between 1.3 and 2.9 percent. In fact, it was less than in the white individuals.

In 344 as part of the exclusion criteria the darker skinned individuals were excluded, mostly for reasons of ascertainment, but the clinical trial database was very reassuring that, if anything, there may have been a lower rate.

DR. LEGGETT: Dr. Wald?

DR. WALD: In any of the clinical trials was the drug continued in patients who developed a rash? If so, what was the outcome?

DR. SHEAR: It was. Gary, do you want to

comment on that?

DR. PATOU: Yes, many of the patients in the original clinical trials actually continued therapy after they developed a rash. It was at the time when we were not aware of an increased rash rate on study. In fact, 75 percent were actually treated through rash and we looked to see if there was any increased severity or adverse events that were associated with treating them through the rash in that regard, and there were not.

DR. LEGGETT: Dr. Poretz?

DR. PORETZ: The rash associated with amoxicillin is exacerbated in people who have concurrent viral infections like EBV. I saw that you obtained EBV serologies. I don't know what they showed but in the patients that you studied, you obviously went to great care to make sure that they had bacterial infections. They had sputa collected or whatever. Were patients put on gemifloxacin who had coexistent viral illnesses, and was there a greater incidence of rash? Because in a younger population, young women below the age of 40, I will bet you in the community people will be put on a drug like this when they have a viral illness and not necessarily a bacterial problem.

DR. SHEAR: Just to reinforce that, in study 344 these were healthy volunteers who did not have infection and who were given the drug and it was done in a very controlled way, which actually made it easier because you didn't have to worry about how they were doing clinically.

Epstein-Barr, EBV, was looked at and there was no positive EBV. One could argue that maybe other infections should be looked at as being reactivated, or whatever. That is an area that is still very much investigational in trying to understand exanthems, but that wasn't found in that study. As far as in a larger clinical trial database, Wayne, did you want to speak to that? Wayne Danker is the senior medical advisor for Parexel.

DR. DANKER: In the clinical trial database the only pathogens that were looked for were the typical respiratory pathogens that one would seek for a claim for the antibiotic. So, specimens were not specifically looked at for viruses or cultured for viruses.

DR. PORETZ: But in individuals who have been treated in some parts of the world, Europe or somewhere, there must be data on those people who

had coexistent viral infections perchance.

DR. DANKER: It wouldn't have been captured on the CRF-1. The only things that were captured on the CRF-1 were the sputum culture results from the AECB and the CAP patients.

DR. LEGGETT: Dr. Proschan?

DR. PROSCHAN: I have a comment that is not about rash. I don't know whether you want to delay that.

DR. LEGGETT: Can we delay that?

DR. PROSCHAN: Sure.

DR. LEGGETT: Dr. Patterson?

DR. PATTERSON: Since the anti-pneumococcal quinolones are more similar in structure to each other than, say, cipro., would cross-sensitization be more likely if gem. was compared to, say, gati. than to cipro.? I guess the corollary to that is do you know what part of the gem. molecule is associated with this rash? Is it present in the other anti-pneumococcal quinolones?

DR. SHEAR: That is a very good question. I think perhaps Dr. Werner Pichler, who has worked with the quinolones and rash and has done some very good work on that, could come and speak to that.

DR. PICHLER: Patients who were treated with ciprofloxacin and generated T-cell clones against these compounds were analyzed for cross-reactivity with 7 different fluoroquinolones. We found that the majority of the T-cell clones reacted only with the original compound which was ciprofloxacin or norfloxacin. But some clones reacted also with a variety of different fluoroquinolones. So, in principle there is the chance that there is cross-reactivity but the cross-reactivity becomes clinically manifested only if you have a very strong immune reaction to first line and if you have many, many clones which react with these compounds. The majority of clones react only with the original compound. It is quite complicated.

DR. LEGGETT: Good. Can we take a break now and come back in ten minutes? Could I please speak with a representative from the company?

[Brief recess]

DR. LEGGETT: Hello again. The next part of today's proceedings will be the FDA presentation. To give us a brief introduction will be Dr. Ed Cox.

FDA Presentation

Introduction

DR. COX: Good morning and almost good afternoon. I am Ed Cox. I am the Deputy Office Director for the Office of Drug Evaluation IV.

[Slide]

Today what I am going to do is to just review the structure of the FDA presentation just to orient folks. We will start out with a presentation by Mr. Pete Dionne who will be reviewing the microbiology; followed by Regina Alivisatos who will be talking about community-acquired pneumonia; and then Eileen Navarro will be talking about acute bacterial exacerbation of chronic bronchitis; followed by Dr. Maureen Tierney who will be talking about safety. Then I will just come back and make some brief remarks at the close of the presentation.

With that, I will turn the microphone over to Mr. Dionne. Thank you.

Microbiology

MR. DIONNE: Good morning. I guess it is still morning.

[Slide]

I am Pete Dionne and I get to start off FDA's presentations on gemifloxacin. In the next

few minutes we will be talking about gemifloxacin's microbiology from the FDA viewpoint.

First of all, we will look at the activity of gemifloxacin to compare to some of the other quinolones, mainly against the major respiratory tract infections. After that we will look at the activity of gemifloxacin and compare it against certain resistant Strep. pneumoniae strains. Then we will look at the comparative activity against genetically defined mutants of Strep. pneumo. Lastly, we will look at the efficacy of gemifloxacin and some comparative quinolones in a rat pneumonia model.

[Slide]

On this first slide I have listed the MIC-90s for gemifloxacin and some of the other comparative quinolones. As you will notice, against the gram positive organisms gemifloxacin's MIC-90s are considerably lower than most of the other quinolones. Against the gram negative organisms the MICs are comparable to most of the other ones.

Another point you might want to consider is against E. coli and Klebsiella, gemifloxacin's MIC is higher for these two organisms. That may

affect how well it works against these two organisms in clinical efficacy.

[Slide]

As you know, looking at MICs alone is only one part of the thing we have to look at. If we look at the AUC, which most people think with quinolones is the important PK parameter, we notice that gemifloxacin's MIC is about 4-8 times lower than those for the other comparative quinolones. It is basically about 6 times lower than that for moxifloxacin.

[Slide]

Let's see what we have just reviewed here. We noticed that gemifloxacin's MICs are lower against the gram positive bacteria compared to other quinolones. Then we have noticed that gemifloxacin's MICs are about equal to other quinolones against the gram negative bacteria. Gemifloxacin's PK parameters weaken the significance of the lower MICs against the gram positives. Gemifloxacin's PK parameters may affect the efficacy against the enterobacteriaceae.

[Slide]

On this slide we have looked at Pen-resistance to Strep pneumo. The thing to

notice here, as has already been presented this morning, is the MIC values and the Pen-resistant ones are basically equal for all the quinolones.

[Slide]

On this slide we look at quinolone resistant Strep pneumo. Notice that there is a difference here, as you would expect. The quinolone-resistant ones for gemifloxacin have MIC-90s of 0.25-1.0 with a median MIC-90 of 0.5 as compared to 0.06 for the quinolone susceptibles. Notice this is only one study. Moxifloxacin has an MIC-90 about 4 in this study and levofloxacin and ciprofloxacin have considerably higher MICs against these quinolone-resistant ones.

[Slide]

On this slide we look at some genetically defined Strep. pneumo. mutants. As was pointed out this morning, ParC doesn't affect gemifloxacin's MICs too much. They go up about 2-4 times. Moxifloxacin's run about the same, but levofloxacin's go up considerably. The shaded value here represents the double mutant. As you can see, gemifloxacin's MIC is 0.25, moxifloxacin's is about 2.0, levofloxacin and ciprofloxacin are greater than 32.

[Slide]

On this slide we have some ciprofloxacin Strep. pneumo. and we have done MIC testing against them. We have also genetically defined the mutations. What you might want to notice here is that this one is ciprofloxacin intermediate. It also has no mutations. So, that may indicate that ciprofloxacin is probably one of the better drugs for Strep. pneumoniae. The ones shaded here are the double mutants. Once again, gemifloxacin's MIC is 0.12 to 0.25; moxifloxacin's is around 2, gatifloxacin is 4; levofloxacin is 8 and ciprofloxacin is 60.

[Slide]

This experiment we saw a little bit of this morning. What happened, there were 44 Strep. pneumoniae second step mutants. In this slide I have listed, out of the 44, the numbers of each of the MICs. As you can see, most of the ones for gemifloxacin are around 0.25. Moxifloxacin's majority was 2; gatifloxacin was 1 higher and levofloxacin and ciprofloxacin were considerably higher than that.

[Slide]

Now if we look what we have learned in the

second part, we see that Strep. pneumo. MICs, as expected, against the Pen-resistant ones were the same as the Pen-susceptible for all the quinolones. When we get to the quinolone-resistant Strep. pneumo. gemifloxacin's MICs are in the range of 0.25 to 1.0 and moxifloxacin's--granted, it was only one study--was around 4. The Strep. pneumo. double mutants had gemifloxacin MICs, once again, of 0.25. Moxifloxacin's were around 2 and levofloxacin's was 32. If you consider that gemifloxacin's value is about 6 times the AUC, about 6 times lower than the moxifloxacin's and you multiply 0.25 by 6 you get 1.25, which is approximately what moxifloxacin's MIC is for these double mutants.

[Slide]

Lastly, we are going to look at the efficacy of gemifloxacin and comparative quinolones in a rat pneumonia model, Strep. pneumoniae being the infecting organism. On the first slide all the gemifloxacin MICs are less than equal to 0.03 mcg/ml. Some of them are Pen-resistant, some are macrolide resistant. If you notice gemifloxacin, the level of detection in this experiment was less than or equal to 1.7 CFUs per lung.

Also, dosing in this experiment was once daily and started 24 hours after the infection was started. This will be significant when we go to the other slide. Dosing was once daily because most of the quinolones, as you know, are dosed once daily and they tried to represent the same AUC values in this experiment as what would happen with a normal human dose.

When they tried this experiment with gemifloxacin's MICs of 0.125, they didn't get efficacious results. So, they looked at it and they said, well, the half-life in the rat is about half of what it is in humans so they went to twice a day dosing, kept the dose per day the same but just went to twice a day dosing. The shaded area represents gemifloxacin's MICs of 0.25 and there were 5 of those. For 3 of them gemifloxacin wasn't any better than the control.

Once again, you might want to notice that in this experiment gemifloxacin never got down to the level of detection for most of these. They were better than levofloxacin for almost all cases.

[Slide]

The last slide in this series compares gemifloxacin with moxifloxacin and gatifloxacin.

Once again, dosing was b.i.d. As you can see, when you get the gemifloxacin MICs of 0.03 or less once again you get to the level of detection for gemifloxacin but moxifloxacin and gatifloxacin were pretty much the same. Gemifloxacin beat moxifloxacin in a couple of cases. It was better than gatifloxacin also in other cases. But overall, the efficacy in this experiment appears to be pretty equal for all three of them.

[Slide]

In this rat Strep. pneumoniae infection model isolates for gemifloxacin MICs less than or equal to 0.03 mcg/ml were able to be dosed once daily, and the CFUs reached close to the level of detection. Isolates with gemifloxacin's of 0.125 mcg/ml had to be dosed twice a day and the efficacy never got down to the level of detection. In most cases in these experiments gemifloxacin appeared to be better than levofloxacin and gemifloxacin appeared to be about the same as moxifloxacin and gatifloxacin.

[Slide]

The summary that I have is that gemifloxacin, at least from the microbiological viewpoint, looks to be about equal to moxifloxacin

and looks to be better than levofloxacin.

With that, I will turn the podium over to Dr. Alivisatos to talk to you about community-acquired pneumonia.

Community-Acquired Pneumonia

DR. ALIVISATOS: My name is Regina Alivisatos and I will be presenting the FDA perspective on the efficacy of gemifloxacin in the treatment in community-acquired pneumonia.

[Slide]

The sponsor's proposed indication is community-acquired pneumonia caused by Streptococcus pneumoniae, including penicillin, clarithromycin and cefuroxime-resistant strains, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila and Staphylococcus aureus. The proposed dose and duration of treatment is one 320 mg daily for 7 days.

The sponsor is requesting duration of treatment of 7 days primarily for two reasons: One, because the incidence of rash increases with durations of treatment greater than 7 days. Two, because of the movement toward shorter durations of

treatment in respiratory tract infections.

[Slide]

I would like to start off by saying that the FDA is in general agreement with the sponsor's efficacy analyses. The FDA presentation will concentrate on efficacy in relation to the duration of treatment and to the severity of disease. I will also present the data that was reviewed by the agency in support of the sponsor's claim of efficacy versus Streptococcus pneumoniae, including penicillin-resistant, macrolide-resistant and cefuroxime-resistant Streptococcus pneumoniae. I will also briefly mention data submitted regarding quinolone-resistant Streptococcus pneumoniae.

[Slide]

As seen in the sponsor's presentation, there were 6 studies that comprised the clinical studies data set, 4 controlled and 2 uncontrolled. One uncontrolled study, number 287, is ongoing and an interim report was part of the submission. Three of the controlled studies, number 011, 012 and 0149, were randomized, double-blind, parallel group studies and one study, number 185, was an open, controlled trial.

Of interest to the agency was the duration

of treatment. As you can see, only study 011 of the controlled studies, as well as the 2 uncontrolled studies, have a fixed 7-day duration of treatment. Whereas, in 3 of the controlled studies, 012, 049 and 185, the decision to allow dosing to continue to 14 days was made in a non-randomized fashion based on post-randomization efficacy information. Treatment could have been extended at the investigator's discretion at the on-therapy visit, for example if the pneumonia was confirmed or if it was due to an atypical pathogen such as Legionella.

[Slide]

The agency, although in general agreement with the sponsor's analyses, determined that combining the 7-day data from the subjects enrolled in the fixed 7-day trials with those that received 7 days in the 7-14 day trials should not be done because the 7-day data from the fixed 7-day trials contain information from all patients enrolled in those studies, while the 7-day data from the 7-14 day studies have patients removed who were considered by the physicians to have needed more treatment and could, in general, represent a more ill population. This would cause the 7-day

efficacy data from these studies to be biased most likely upwards.

In our presentation of the data we will not combine these 2 groups of 7-day duration subjects. Since the sponsor is interested only in a 7-day regimen, we considered the data from the 7-day fixed regimen as primary data, with the 7-14 day data as supportive. Although the sponsor didn't mention this today, they did have it in their submission, as cautioned by them, the 7-day efficacy data should not be directly compared to the 14-day efficacy data. Each group of gemifloxacin patients should only be compared to their respective controls.

[Slide]

There were 1349 intent-to-treat patients treated with gemifloxacin and 927 treated with an active comparator, and 947 patients were treated with gemifloxacin in the controlled studies and 402 patients were treated with gemifloxacin in the uncontrolled studies; 569 patients, 1167 from study 011 and 402 from the uncontrolled studies, had a fixed 7-day duration of treatment; 468 patients from the controlled 7-14 day studies received 7 days of treatment and 312 patients received greater

than 7 days and in some cases up to 14 days. Overall, 312 of 947, or about a third of the controlled study patients received greater than 7 days of treatment.

You have seen the sponsor's primary efficacy analyses and we are not going to repeat them all. I will be presenting additional analyses that the FDA performed that handled the fixed 7-day duration alongside those that received a duration of 7-14 days.

[Slide]

The FDA performed analyses of clinical response at the test of cure or the follow-up visit by age, race and gender, as well as by study and duration of treatment. As can be seen in these analyses of clinical response by duration of treatment, when the allowed comparisons were made between treatment groups for both the 7-day fixed and the 7-14 day studies, clinical success rates were similar to those of respective comparators.

Again, I would like to remind you that because the sponsor is requesting a 7-day treatment duration it is most appropriate for us to base our regulatory decisions on the data from the 7-day fixed studies, and the data from the 7-14 day

studies should be considered as supportive.

[Slide]

For the purposes of this submission, severity was determined by categorizing patients according to the mortality risk classes published by Dr. Fine. These criteria were applied retrospectively except for ongoing open study 287 where they are being applied prospectively. Patients were assigned to one of five classes with respect to the risk of death within 30 days, first according to an algorithm to class I, and then on the basis of the total point score to classes II through V. A prediction rule assigned points based on age and the presence of coexisting disease, abnormal physical findings and abnormal laboratory findings at presentation.

Based on assigned risk class, patients were classified as having mild, or classes I and II, moderate, class III, or severe, classes IV and V, disease. Patients in risk classes I through III can often be managed as outpatients, whereas those in classes IV and V are at higher risk of death and often required hospitalization.

[Slide]

Demographics were also assessed on all

patients by degree of severity. And, 996 or 7.14 percent of patients had mild disease. In this group there were more females than males. The mean age of this category of patients was 46.6 years. Those patients with moderate and severe disease were predominantly males and older, with a mean age of 69.4 years for the moderately ill gemifloxacin-treated patients and a mean age of 76.3 years for the severe group of gemifloxacin-treated patients.

The severe group of patients represented 7.2 percent of the 7-day fixed population, 9.6 percent of the 7-day group of the 7-14 day population, and 13.8 percent of the 14-day population. Thus, there was an increased number of severely ill patients in the more prolonged duration treatment group and there were fewer severely ill patients in the fixed 7-day treatment group.

Of the 129 intent-to-treat patients categorized as having severe disease, 125 had class IV disease and 4 had class V disease. The sponsor provided further details on these patients regarding intubation status, use of pressors or respiratory treatments at the time of enrollment

and none of the subjects had documented use of any of these at that time. Six subjects ultimately did require at least one of the concomitant treatments during the study and all of those patients ultimately failed treatment.

[Slide]

When clinical response was assessed at the test of cure by severity, success rates for those patients with mild and moderate disease were similar to those of the overall population. Although efficacy in the severely ill patients was high, there were very few patients, 26 in total, treated with a 7-day fixed regimen.

As noted previously, the 7-day group of the 7-14 day studies should not be added to the fixed 7-day patient population and, again, comparisons should not be made between the 7 and the 14 day regimens. So, in the agency's viewpoint, the data currently available on severe patients are limited.

[Slide]

In addition to the classification of subjects by defined criteria, the sponsor also assessed clinical response in hospitalized subjects, thus using hospitalization as criteria to

assess the effectiveness of gemifloxacin in severe cases of community-acquired pneumonia. However, as the decision to hospitalize or not was investigator driven and may have varied according to geographic location, it would not appear that the presence or absence of this factor can be used as a sole determinant of severity of illness.

Only in open, controlled study 185 were all patients hospitalized for at least the first 24 hours of treatment. In that study, 36 of the 172 gemifloxacin-treated patients were classified as having severe disease or Fine classes IV and V, whereas approximately 80 percent of the patients in that study had mild to moderate disease, again raising the question of the appropriateness of using hospitalization alone as criteria for severe community-acquired pneumonia. When allowed comparisons were made between gemifloxacin and the comparator regimens, clinical response rates were similar.

[Slide]

The sponsor provided a separate analysis of clinical response in bacteremic patients. There were 48 gemifloxacin-treated patients or 4.7 percent of the combined all studies data set with a

positive blood culture at screening. In the agency's analysis of bacteremic patients, although clinical response rates were comparable between treatment arms, the sample size was too small to allow for valid comparisons. Clinical response for all bacteremic patients receiving the fixed 7-day regimen was 91 percent, whereas for all 7-14 day patients it was 96.3 percent. In that group 4 subjects received a 7-day treatment regimen.

[Slide]

The clinical review team requested that the sponsor provide tables of risk class specific mortality for all intent-to-treat patients. Overall mortality was similar between the gemifloxacin and comparator treated groups, as well as between the gemifloxacin controlled and uncontrolled study patients, with 12 deaths, or 1.3 percent, in the gemifloxacin controlled study patients; 13 deaths, or 1.4 percent, in the comparator treated patients; and 5 deaths, or 1.2 percent, in the gemifloxacin-treated uncontrolled study patients. There was a total of 17 deaths, or 1.3 percent, in all gemifloxacin-treated patients.

When deaths were assessed by Fine class, it appeared that mortality rates for classes I, II

and III patients were consistent with what was expected based on the publication by Dr. Fine. In class IV patients the mortality rates in the clinical studies, which are here, appeared to be somewhat less than what was reported for Fine class IV patients. There were too few class V patients in the data set to draw any conclusions for this class.

[Slide]

With regards to regulatory precedents, there are two quinolones at present, levofloxacin and moxifloxacin, that have a severe disease claim and both have oral and intravenous formulations. The criteria for determining severity differed in both applications but in both they were applied at the time of randomization and were used to determine the mode of treatment as well as the duration of treatment. Almost all of the severe patients in the levofloxacin NDA received intravenous treatment and the moxifloxacin claim was granted after FDA review of the intravenous formulation.

[Slide]

To turn to another issue, the sponsor is requesting approval for penicillin-resistant,

macrolide-resistant and cefuroxime-resistant Streptococcus pneumoniae, and has also submitted data regarding quinolone-resistant Streptococcus pneumoniae. At present, levofloxacin and now moxifloxacin have the indication of penicillin-resistant Strep. pneumoniae and no antimicrobial currently has a macrolide-resistant indication, although it has been discussed.

As you heard earlier, Dr. Powers, of ODE IV, gave some introductory remarks regarding the FDA perspective on the issue of multi-drug resistant Streptococcus pneumoniae to this committee. Points that were raised in his presentation today, as well as at the January, 2003 Anti-Infective Advisory Committee meeting, and that continue to need to be addressed are what is the clinical relevance of macrolide-resistant Streptococcus pneumoniae? Should it be treated as a separate entity from penicillin-resistant Streptococcus pneumoniae? Should an approval be granted for both or for multi-drug resistant Streptococcus pneumoniae or only for penicillin-resistant Streptococcus pneumoniae?

In addition to these questions, the issue of cefuroxime-resistant isolates also now needs to

be addressed. What is the clinical relevance of this organism? As you will see, all penicillin-resistant Strep. pneumoniae isolates in this submission were also cefuroxime resistant and these isolates represented 67 percent of the total number of cefuroxime-resistant isolates. Also, 83 percent of cefuroxime-resistant isolates were also macrolide resistant.

[Slide]

The agency and the sponsor are in general agreement with regard to numbers. We had 12 per protocol gemifloxacin-treated patients who had Strep. pneumoniae isolates with penicillin MICs of greater than or equal to 2 mcg/ml and 3 of these had MICs of 4 mcg/ml. The clinical success and bacteriological eradication rates in patients with PRSP were 100 percent. Four comparator arm patients had penicillin-resistant isolates with 100 percent clinical success in bacteriologic eradication rates.

[Slide]

We are also in agreement that 25 gemifloxacin-treated per protocol patients with Streptococcus pneumoniae had macrolide-resistant isolates, defined as clarythromycin MIC of greater

than or equal to 1 mcg/ml. Clinical success and bacteriological eradication rates were 88 percent, and 10 of these isolates, or 40 percent, were also penicillin resistant.

There were 12 comparator treated per protocol patients found to have macrolide-resistant Streptococcus pneumoniae, with clinical success and bacteriologic eradication rates of 91.6 percent. Three of these isolates were also penicillin resistant and 2 of those 3 were successfully treated.

[Slide]

Eighteen patients had cefuroxime-resistant Streptococcus pneumoniae, defined as a MIC of greater than or equal to 4 mcg/ml. Clinical success and bacteriological eradication rates at follow-up were 94.4 percent. Twelve out of the 18 cefuroxime-resistant isolates were also penicillin resistant, or 67 percent, and 15 of 18 cefuroxime resistant isolates were also clarythromycin resistant, or 83 percent. On the comparator's arm there were 7 patients with Streptococcus pneumoniae isolates resistant to cefuroxime that were all successfully treated.

[Slide]

Finally, regarding quinolone-resistant Streptococcus pneumoniae, in the gemifloxacin group of the combined studies population there were no pathogens resistant to ofloxacin and levofloxacin. There was one resistant isolate in the all comparators arm that was a failure. In the gemifloxacin group there were 4 isolates with Streptococcus pneumoniae with an MIC against ciprofloxacin of 4 mcg/ml. All 4 of these were successfully treated.

With that, I will turn it over to Dr. Navarro.

Acute Bacterial Exacerbation of Chronic Bronchitis

DR. NAVARRO: Good morning.

[Slide]

My name is Eileen Navarro, and I am here to present the agency's perspective regarding the efficacy of Factive for the indication of acute bacterial exacerbation of chronic bronchitis.

Before I proceed, I would like to acknowledge the assistance of our statistical colleagues in understanding the sophisticated statistical analyses that were unique to this indication.

[Slide]

The applicant's NDA seeks to establish that Factive is efficacious in the treatment of acute bacterial exacerbations of chronic bronchitis, which I will refer to in the rest of the talk as ABECB, being due to H. influenzae, M. catarrhalis, S. pneumoniae, H. parainfluenzae and S. aureus. There are three things to note that separate this indication from CAP. You will note that the applicant does not seek an indication for resistant isolates in this indication. As has already been alluded to by Dr. Low regarding the prevalence of resistant isolates in chronic bronchitis, this is appropriate to consider.

Another thing that distinguishes this indication is the fact that a shorter duration of 5 days is sought compared to community-acquired pneumonia, and that is important to consider when one looks at the adverse event rates for rash.

The other thing to note is that the applicant submits data regarding additional findings outside of the efficacy for the larger population with ABECB, and one of these findings is actually a claim being made in the label of earlier eradication of H. influenzae from the sputum. So, within the context of this indication, we are being

asked to understand the significance of the eradication of bacteria from the sputum.

[Slide]

The applicant's additional findings, for which no claims are made in the label, are described in the applicant's background package. This includes superior clinical efficacy in the intent-to-treat analysis; prolonged exacerbation-free intervals; and several findings that relate to efficacy in severe hospitalized ABECB, including efficacy in hospitalized patients obviating the need for intravenous therapy; earlier time to hospital discharge; and reductions in hospitalization due to respiratory tract infections.

Particularly for an indication where there are several treatment alternatives, it is important, and in fact it is innovative to look at what the additional benefits may be due to a drug and that has been rightly described by the applicant. We will, however, attempt to describe these findings in the context of the study design and the study objectives; describe whether the finding is one prespecified primary endpoint or one of several secondary endpoints and whether

adjustments have been made for multiple comparisons. More importantly, we will look at the clinical implications of these findings and end with a discussion of additional considerations for antibacterial use for this indication.

[Slide]

The pivotal studies find that Factive was non-inferior to study comparators in the treatment of ABECB. The agency agrees with this conclusion based on point estimates that were well within the prespecified limits of inferiority. Two other supportive and several ancillary studies support the conclusion of non-inferior efficacy.

[Slide]

I will now move to the additional findings. The applicant's findings that Factive results in earlier bacterial eradication--I am sorry, I think I have the wrong slide here. I am not used to this new mouse that we bought only a few days before this presentation.

[Slide]

The applicant's finding that Factive results in earlier bacterial eradication compared to clarythromycin was based on unadjusted analysis in the pivotal study 068 and in study 105. Were we

to consider this analysis as statistically significant, although questions still remain regarding the relevance of earlier bacterial eradication in ABECB.

We note that patients with H. influenzae represented only a small proportion of patients who fulfilled the inclusion criteria for ABECB in the pivotal study. For example, please note that there were 24 patients out of the 600 patients in that study that actually led to this conclusion. Nevertheless, in the small subgroup of patients in whom eradication of H. influenzae was proven, early eradication did not correlate with additional benefit over the comparator-treated patients in whom eradication of H. influenzae was delayed.

In addition, in study 105 early eradication may be related to the pharmacokinetic differences noted in that study between Factive and the comparator erythromycin. To also put this in a larger perspective, please note that bacterial eradication favored the other comparator, levofloxacin, in some of the pivotal studies presented earlier.

[Slide]

Now we are back to this slide. The

finding of superior clinical efficacy in the intent-to-treat analysis is derived from studies 068 and 207 where the point estimates favored Factive and the lower bounds excluded zero, with a value of 0.9 for study 068 and 0.7 for study 207.

[Slide]

The applicant's finding of superiority was limited to the ITT analysis in the supportive studies 068 and 207. In the same studies the primary analysis of clinical efficacy in the per protocol population showed that Factive was not inferior to the study comparators, and the secondary analyses of bacterial efficacy in the patients with pathogens showed similar efficacy rates. In the pivotal studies Factive was non-inferior in clinical efficacy for the analytic populations for ITT and per protocol, and the bacterial efficacy rates in both populations were also similar.

[Slide]

The finding that Factive was at least as good as parenteral therapy in severe ABECB is derived from study 207. Patients in study 207 were older, had more frequent ABECB exacerbations and more often required oxygen and corticosteroids than

the patients that were described in the pivotal studies, supporting the finding that Factive was non-inferior to parenteral therapy in patients with these demographics. However, it is important to note that this open-label, non-U.S. study enrolled patients with severe ABECB who were able to tolerate oral medications. This is a population that is more restricted than all patients requiring parenteral therapy.

Another question raised by the study is whether parenteral therapy is needed for patients who are able to tolerate oral medications, and whether patients so treated in this study would be analogous to a hospitalized patient population in the U.S.

I think it was Dr. Shear who pointed out that hospitalization for a rash may be different in certain countries, and the question we raise is whether these findings from a non-U.S. study may be relevant to the way we hospitalize and treat our patients with ABECB.

The applicant also shows that Factive-treated patients were discharged a mean of half a day earlier than patients that received parenteral therapy. This difference in mean time

to discharge could be accounted for by the time required to insert and then remove intravenous access in patients that receive parenteral therapy. No difference was found in the primary outcomes of clinical efficacy.

More importantly, related outcomes such as the rate of symptom resolution and indirect patient costs were no different between treatments, making it difficult to understand what the excess duration of treatment was related to. Furthermore, this analysis was only marginally significant using the Wilcoxon test, not significant using log rank test and the hazard ratio was not significantly different than 1.

[Slide]

Time to next exacerbation was evaluated in three studies. The findings from these studies were contradictory, with study 139 trending favorably for Factive and study 105 favoring the comparator. In study 112, where this analysis was the only primary outcome of interest and did not require adjustments, time to exacerbation for Factive was not significantly different from the comparator.

Respiratory tract related hospitalization

was similarly evaluated in these same three studies, although the applicant presents only the results from study 139. The finding of reduced hospitalization in Factive-treated patients was similarly unadjusted for multiple comparisons and other related outcomes do not buttress this conclusion.

[Slide]

This slide is a partial list for approved products for ABECB. It is important to note that, while in several classes antimicrobials limited to those that are used for oral therapy for ABECB are indicated for the treatment of ABECB, only three are registered as 5-day treatments for this indication. Moxifloxacin and gatifloxacin are both approved as 5-day therapies and as 7-day therapies for CAP.

Please note further that quinolone antimicrobials listed here account for a good number of the available alternatives for ABECB. An issue that needs to be addressed in assessing the risk-benefit of Factive is the potential that a patient is labeled quinolone allergic on the basis of a rash, or becomes cross-sensitized to subsequent quinolone use. Elimination of the

quinolones as a therapeutic alternative would significantly impact ABECB to a far greater proportion than it would patients with community-acquired pneumonia because patients with ABECB do have multiple recurrences, each requiring repeated exposures to antibiotics.

[Slide]

This slide compares the age-specific use of antibiotics for chronic bronchitis in the community to that in the clinical trials submitted by the applicant. The utilization data shown here represent a 3-year average of antibiotic use for bronchitis from the study by Scott and Levin, an appendix A of the applicant's background package.

The study indicates that 33.5 percent of prescriptions for bronchitis would be written for patients under 40 years of age. Compared to this, the age distribution of patients in the pivotal ABECB studies was less than 1 percent of patients so treated in the clinical trials.

In assessing the risk-benefit of Factive for ABECB, one consideration to take is the difference in the conditions of use within the context of a clinical trial and the anticipated broader use of the drug once it is available in the

community.

[Slide]

We conclude that the clinical efficacy of Factive in ABECB is as good as its comparators. While we laud the applicant for their innovative analysis of trying to define additional benefits for the drug, we find that questions remain regarding the clinical relevance or applicability of the additional findings in the treatment of ABECB. In addition, the evidence supporting other findings is limited by the study design issues or could be attributed to chance alone.

Finally, the antibiotic usage for bronchitis does have implications in the community far beyond just effectiveness, as Dr. Mandell has rightly pointed out, and the impact on available therapeutic alternatives is a relevant consideration in evaluating the data presented for the efficacy of Factive.

Safety

DR. TIERNEY: Hello.

[Slide]

My name is Maureen Tierney, and I am here to present the safety of Factive, or gemifloxacin, from the FDA's viewpoint.

[Slide]

This first slide shows the makeup of the safety population that was used to evaluate the safety of gemifloxacin. It was a combination of Phase II and Phase III clinical trials, totaling 6,775 patients for gemifloxacin and 5,248 patients for comparators, which included beta-lactams, macrolides and other quinolones.

As has already been mentioned, these include patients only who received 320 mg of gemifloxacin. Individuals were enrolled in these studies for the treatment of a variety of conditions, but for the two indications being looked at here, ABECB was approximately 45 percent of the combined clinical population and CAP 17.5 percent. I will refer to this population as the combined clinical population unless I note otherwise looking at other clinical pharmacology studies of higher doses of study 344.

[Slide]

The demographics of the safety population show that approximately 20-25 percent of the individuals in total were under 40; about 45 percent between 40 and 65; and between 30 and 35 percent over 65.

[Slide]

There was a mild preponderance of women in both arms.

[Slide]

The breakdown by race shows between 87 and 92 percent white; between about 3.5 and 4.5 percent black; 1 to 3 percent oriental and 4 to 6 percent other, which includes individuals who are Hispanic.

[Slide]

I am going to concentrate my talk today on four areas: Adverse events of special interest and that will include withdrawals and serious adverse events; QT prolongation; the hepatic safety profile of gemifloxacin; and rash.

[Slide]

When looking at withdrawals due to adverse events, rash was the most common cause of withdrawal from the gemifloxacin arm, causing 0.9 percent of the patients to be withdrawn versus 0.3 percent for comparator. Related cutaneous events of urticaria reveal 0.2 percent or 15 being withdrawn from the gemifloxacin arm versus 4 or 0.1 percent for comparator. The other more common causes of withdrawals, nausea, diarrhea and vomiting--gastrointestinal side effects were more

common in comparator as compared to gemifloxacin.

[Slide]

Serious adverse events that were considered by the investigator to be of suspected relationship to drug medication showed that rash was the most common cause of the serious adverse events in the gemifloxacin arm for 7 cases, as has already been described by Dr. Shear, versus 1 for comparator.

LFTs being increased were the cause of serious adverse events in 3 patients receiving gemifloxacin versus none for comparator. Pneumonia was pretty even between the 2 groups. No patients were removed from the gemifloxacin arm for severe diarrhea but 3 from comparator.

[Slide]

We will talk about QT effects for some of the reasons already mentioned. It is a known side effect for the quinolone class. There was some mild prolongation noted in the database and it would be a serious event if it occurred, but I would like to note now that there were no cases of Torsade de pointes noted in the gemifloxacin database.

[Slide]

When looking at QT effects trying to assess preclinically the potential of a drug for QT prolongation, several assays are looked at, including Perjinki and inhibition of hERG. This slide is shown not to give a ranking of the variety of quinolones but in this and other assays gemifloxacin was in the mid range or the ball park of other quinolones for its potential for QT prolongation.

[Slide]

The mean changes in QTc in the clinical pharmacology population, a large percentage of which were women in study 344, was 4.9 milliseconds of increase and in the combined clinical population, 2.6 milliseconds.

[Slide]

This slide looks at changes in QTc from baseline. In the end, where you see sort of larger increases from baseline, 50-60 and over 60, there is a trend towards a few more patients in the gemifloxacin arm.

[Slide]

This slide shows the relationship of gemifloxacin dose and QTc. It is the result of a meta-analysis of five studies. These are five

Phase I studies looking at both old and young healthy individuals receiving 320 mg, 480 mg or 640 mg doses of gemifloxacin. In single doses there was no dose effect seen, but in multiple doses--

I would just like to orient you. On the X axis is the dose of gemifloxacin and here is the maximal change in mean QTc, so the average maximal change in mean QTc. At 320 mg there is a change noted of minus 5 milliseconds; at 480, plus 5.5 milliseconds; and at 640 the increase is plus 16 milliseconds.

[Slide]

As Dr. Patou mentioned, when you talk about QT it is important to discuss issues of drug interactions. There is no inhibition or induction of CYP450 enzymes by gemifloxacin nor is it dependent upon its metabolism by the CYP450 enzymes. It also has a dual route of elimination.

[Slide]

I would now like to move to the hepatic safety profile of gemifloxacin. We will talk about four areas, the preclinical findings with the drug; LFT increases that were seen at higher doses; LFT increases in those with hepatic impairment or more comorbidity; and ALT and/or bilirubin elevations.

[Slide]

When looking at preclinical hepatic findings in dogs, and these were in repeat oral dose studies for 28 days, for 3 months or 6 months, cholangitis and pericholangitis with hepatocellular degeneration and single cell necrosis was seen at high doses. This was associated with crystalline deposits of drug in the bile canaliculi and was associated with concomitant elevated ALT and alk. phos. These elevations, however, did return to normal after 4 weeks.

[Slide]

When looking at individuals who got higher doses and, remember, these are not the individuals in the combined clinical populations, there was an uncomplicated UTI study looking at mostly younger women who were randomized to receive gemifloxacin 640 mg in a single dose versus ciprofloxacin 250 mg b.i.d. for 3 days. Of the 592 individuals who received gemifloxacin, 9 or 1.6 percent had ALT elevations greater than 2 times the upper limit of normal and 4 had greater than 6 times the upper limit of normal. There were no similar ALT elevations seen in comparator. There were no significant bilirubin elevations in either group.

Similar results were seen in the 480 and 640 dose clinical pharmacology studies, in particular study 005 which was a PK study in healthy elderly individuals, 4 of 16 of whom were required to be withdrawn because of elevated ALTs, with ALTs ranging from 121 to 33 on therapy.

[Slide]

Dr. Patou also discussed the issue of hepatic side effects in individuals with baseline liver disease. This slide shows adverse events of the liver and biliary system in patients with baseline liver disease who were defined as individuals who had a history of liver disease and, in addition, had elevated ALTs at screening.

The gemifloxacin N of 235 does include some patients who were in non-comparative studies. These are adverse events of hepatic enzyme increase seen in 3.4 percent for the gemifloxacin arm and none for comparator; 4.3 percent in alkaline phosphatase elevations for gemifloxacin versus none for comparator, and 2.1 percent bilirubin increase versus 0.6 percent for comparator.

[Slide]

When looking at individuals who may have higher comorbidity, there are 2 studies I would

like to mention. Study 185 is a study looking at patients with CAP requiring hospitalization so, in general, a more ill population. Of the patients who received gemifloxacin there were 6 with LFT elevations greater than 3 times the upper limit of normal, with 4 of those being withdrawn; and 3 with LFT elevations greater than 3 times the upper limit of normal in the comparator arm but none requiring withdrawal.

In study 287, which is not a study in the combined clinical database but is an ongoing clinical study which is trying to enroll patients only with pneumococcal pneumonia, there were 2 individuals seen who had ALTs greater than 3 times the upper limit of normal with a concomitant bilirubin greater than 1.5 mg/dl.

[Slide]

I would now like to look at things just from the biochemical standpoint. As a result, I may repeat some of the data in prior slides. When looking at combinations of ALT and bilirubin, as Dr. Patou mentioned, the combination is supposed to be more suggestive of hepatocellular damage. What exactly is the right threshold to look at is unclear and I have seen a variety of different Hy's

rules mentioned.

When looking at ALTs greater than 3 times the upper limit of normal with a bilirubin greater than 1.5, there were no patients in the combined clinical database who received gemifloxacin who met that criteria; and 2, as I just mentioned in study 287; and there was 1 in the comparator arm. That is in the combined clinical population.

If you lower your threshold to a very conservative ALT greater than 2 times the upper limit of normal with a bilirubin greater than 1.5 mg/dl you find additional 3 patients in the gemifloxacin arm in comparative clinical trials and none for comparator.

[Slide]

When looking at bilirubin elevations in isolation, there was 1 healthy male in a clinical pharmacology study whose bilirubin bumped from 0.8 to 7.5 mg/dl. He was asymptomatic and eventually his bilirubin came down to close to normal. But it is interesting to note that he received ofloxacin, for unclear reasons a few months before, whether it was for a clinical indication or another drug study, and had an elevation, though not quite as high, on ofloxacin. There were 3 isolated

bilirubin elevations to greater than 2 but less than 4 times the upper limit of normal in patients who were in range at screening but not for the comparator in the combined clinical population looking at comparative studies.

[Slide]

For ALT elevations alone, there was no patient who was in range at screening who received gemifloxacin who had an ALT elevation greater than 8 times the upper limit of normal on the 320 mg dose. One patient who had an abnormal ALT at baseline of 110 elevated his bilirubin to 501. But there were 2 patients on the 640 mg dose who were in range at screening and who had elevations close to or above 8 times the upper limit of normal.

[Slide]

Lastly, I would like to discuss rash. We are discussing rash today for the reason that it occurred at a higher incidence than all comparators; that there was a higher number of serious adverse events and withdrawals than on all comparators. There was a markedly high incidence in an enriched and carefully studied population of 31.7 percent in study 344 where we saw a large percentage of the body surface area involved,

perhaps more urticaria and 6 percent more mucus membrane involvement, and how these issues would affect clinical practice.

[Slide]

The overall incidence of rash in the combined clinical population was, as you have already heard, 3.6 percent for gemifloxacin versus 1.1 percent for all comparators. There were 7 serious adverse events secondary to rash on the gemifloxacin arm versus 1 for comparator.

Thirty-six patients were reported to have urticaria, or 0.5 percent, in the gemifloxacin arm versus 2 percent for comparator and 64 patients were withdrawn because of cutaneous adverse events from gemifloxacin versus 15 for comparator.

[Slide]

When looking at the severity of rash and the breakdown of that for gemifloxacin versus comparator, I would just like to concentrate on the last line. The rashes were determined to be severe in 13.6 percent of the gemifloxacin arm versus 6.7 percent for comparator. My understanding is that these were severities that were clearly determined by investigator.

[Slide]

You have already seen time and rash. Two-thirds of the gemifloxacin rashes began after day 7, with most of it on days 8, 9 or 10, whereas the comparator rashes in general began on day 7 or before.

[Slide]

The risk factors for rash development are female gender, age less than 40, and a planned duration of treatment of greater than 7 days. The indication appears to be primarily related to these first three explanatory variables and also HRT in women greater than 40 years of age.

[Slide]

I would just like to orient you to this slide. This axis is the percentage of individuals reporting rash and this duration of therapy on the left for gemifloxacin, and on the right for all comparators.

I will discuss based on all the categories, first looking at females under 40 years of age, which is this very light green column. As one increases duration, beginning at 7 days, the rash incidence increases markedly to over 20 percent at 14 days in women under 40 years of age.

I would next like to look at males under

40 years of age, this maroon column, because their incidence appears to go up even more than women over 40 as one increases from 7 to 14 days of therapy.

Females greater than 40 years of age, which is this yellow bar, again start to increase to produce a rash rate probably between 7-8 percent at 14 days. Only the males greater than 40 years of age appear to have a flat incidence regardless of duration.

In the comparator arm rash rates begin to go up to some degree, and even more so at 14 days but, clearly, the impact of duration is not as impressive.

[Slide]

We are looking at the rash rates by indications here. For ABECB the rash rate is 1.5 percent versus 0.8 percent for comparator. For CAP, 4.7 percent versus 2.1 percent for comparator.

[Slide]

I think this slide will show you a little bit why the rash rate of 1.5 percent is seen in ABECB. When looking at the numbers of individuals who were studied, as Dr. Navarro mentioned, we really have very small numbers of women less than

40 years of age, only a total of 8 patients, and for males less than 40 years of age only 7 patients. Clearly, their rash rates are high but the numbers are really quite low.

[Slide]

When looking at females greater than 40 years of age, the total rash rate is 1.9 percent but over 4 percent at 10 days, and for males greater than 40 a total rate of 1.1 percent.

[Slide]

When looking at CAP differentiation by age and by duration in this chart format, clearly there are many more female and male patients under the age of 40 which gives us a more balanced perspective. Looking at females under 40, the rate is 11.6 percent; females greater than 40, 4.6 percent; 5.1 percent for males under 40 and 2.7 percent for males greater than 40. The increase almost doubles, if not more so, going from 7 to 14 days for all of those categories, with the exception of males greater than 40 whose rate appears to stay flat.

[Slide]

HRT use and the risk of rash shows that the incidence approximately doubles with the use of

HRT in women over 40, which has already been mentioned, and gives you an odds ratio of 1.9 which is statistically significant.

[Slide]

The sponsor also looked at prior or subsequent quinolone usage and has already presented this data showing that of 181 patients who received a prior quinolone and then were enrolled in a gemifloxacin study and received gemifloxacin, only 3, or 1.7 percent, developed a rash.

However, this data is subject to a selection bias. Since an individual did not have rash on prior exposure to a quinolone they would be less likely to have rash on subsequent exposure to a quinolone. Secondly, 12 patients who developed a rash on gemifloxacin subsequently received another quinolone for one reason or another. None of those 12 patients developed a rash but this may also be subject to selection bias because had the rash been very severe upon exposure to gemifloxacin, it is less likely they would have received another quinolone.

[Slide]

Now I would like to turn to study 344.

The model has already been shown to you so I will just briefly mention that, again, it was over 1000 healthy women who were randomized in a 5:1 ratio to receive gemifloxacin or ciprofloxacin for 10 days and then, based on which drug they received and whether or not they developed a rash, were further randomized in part B after a 4-week washout period.

[Slide]

The demographics of this show that it was overwhelmingly Caucasian women who were enrolled in the study, 92 percent.

[Slide]

The overall results show that of the 819 women who received gemifloxacin and were evaluated, 260 developed a rash, for a rate of 31.7 percent, with the confidence intervals that are present here. For ciprofloxacin, of 164 women who received cipro., 7 developed a rash, for a rate of 4.3 percent, with this confidence interval.

[Slide]

Withdrawals and severe adverse events that occurred in study 344 showed that of the 819 women receiving gemifloxacin, 26 were withdrawn for a cutaneous adverse event, or 26 out of the 260 who developed a rash, so a 1 percent withdrawal. That

is withdrawal from entering part B; it is not withdrawal from part A since the drug would be stopped in part A. There were none for ciprofloxacin.

There were no rash-related serious adverse events reported in either arm but severe cutaneous adverse events were determined to be present. Again, these were determined by the investigator, 20 out of 260 for gemifloxacin and 0 of 7 for ciprofloxacin.

[Slide]

Time and rash similarly, a later day of onset and a longer mean duration for gemifloxacin related to ciprofloxacin.

[Slide]

The severity of rash, similar to what I just mentioned, 19 patients were determined to have a severe rash, or 7 percent of the gemifloxacin arm; zero for the ciprofloxacin arm, but since there are only 7 patients it is hard to make that comparison.

[Slide]

When looking at the extent of the body surface area that was involved in this rash, the breakdown is shown here but in particular I would

like to point out that over 25 percent of the women who experienced a rash to gemifloxacin had over 60 percent of their body surface area determined to be involved. Of the 7 patients who developed a rash to ciprofloxacin, no one had a rash over 60 percent and they were pretty evenly divided, 4 at 6-10 percent and 1, 11-20 and 1, 21-40.

[Slide]

Looking at the characteristics of the rash, as was described on the rash case report form, clearly, the gemifloxacin rash was overwhelmingly a pruritic rash with erythematous macules and papules. The ciprofloxacin rash description stopped there. No one was described as having any other involvement but in gemifloxacin patients some were described as having plaques, skin tenderness, and 11.5 percent as having urticaria.

I would just like to mention here that of the patients who developed the gemifloxacin rash in part A, there were actually 7 patients who were reported to have fever, 4 who were reported to have eosinophilia, and 1 person who had fever and eosinophilia.

[Slide]

When looking at mucus membrane in part A, of the 7 women who developed a rash to ciprofloxacin, none reported mucus membrane involvement. Of 260 women who developed rash to gemifloxacin, 16 were reported to have mucus membrane involvement. Just to remind you, all of these patients were evaluated not only by the main investigator but by a dermatologist and a very specific form was filled out where the extent of the rash, the description of the rash, the presence of mucus membrane involvement, other systemic signs were requested to be checked or not checked. So, 16 of those case reports included observations of some mucus membrane involvement.

Three of 260 reported eye involvement but on review of those case report forms there were no discrete ocular lesions. It was all dry eyes or very itchy eyes, maybe crusty eyes but no particular ocular lesions. The one person who had genital lesions described was someone who had what was described as a total body rash, and it may have just been extension of that rash as opposed to particular genital lesions.

[Slide]

But 12 of 260 were described as having

mouth lesions. These were described as follows: There were 5 women who were described as having one to a few ulcerations, erosions, papules or vesicles inside the mouth or on the lips; 2, as having erythema on the lips or inside the mouth; 2, as having petechiae on the lips. There were 3 who clearly had mucus membrane mouth involvement checked but either the description is unreadable or unavailable. No pictures were taken of any mucus membrane lesions.

[Slide]

One other aspect of the rash that we looked at was the treatment of gemifloxacin-associated rash both in study 344 and the combined clinical population and, clearly, many women got antihistamines and topical steroids but systemic steroids might be a marker for what an investigator thought was a more concerning versus less concerning rash. Of the 160 women who developed a rash in study 344, 12 of then were treated with systemic steroids, all of which were oral steroids, and 27 of 241 individuals who developed a rash in the combined clinical study were treated with systemic steroids, mostly oral but on occasion with intravenous or IM steroids.

[Slide]

I would now like to turn to discussing a few cases. These cases have been chosen, I would like to say, either because they are more severe cases, there was mucus membrane involvement, steroid treatment was given or a particular histopathologic finding was found. So, they are clearly on the more severe end of the spectrum but since that is what we are concerned about we thought it appropriate to present these cases.

[Slide]

Case one is a 24-year old white female with no past medical history who had onset on day 8 of her rash with associated fever. It was a pruritic rash with erythematous macules and papules covering greater than 60 percent of the body surface area. There were lesions determined to be present in her mouth but were not described. She was treated with Zyrtec and a Medrol pack and the duration of her rash was 6 days. In the quality of life questionnaire that was included for all patients in this study, she determined this very much affected her life.

[Slide]

Her rash is seen here. I believe you may

have seen this earlier today, and her closeup is seen here.

[Slide]

The next case is a 20-year old white female with no past medical history who had onset on day 8 of a pruritic rash with erythematous macules and papules covering greater than 60 percent of her body surface area, also with plaques and mild facial edema. She had erythematous macules present on her lips. She was treated with benadryl and oral prednisone. The duration of her rash was 12 days and her quality of life was moderately affected.

[Slide]

This rash does not project very well but up close one can see that there is quite an extensive rash on her back.

[Slide]

Case three, a 21-year old white female with a history of child asthma, who had onset on day 6 of a pruritic urticarial rash with erythematous macules and papules covering greater than 60 percent of her body surface area. She did not have mucus membrane involvement, was treated with benadryl and oral Solumedrol.

[Slide]

Her rash lasted for 6 days and some aspects of her life were very much affected.

[Slide]

Case four is a 21-year old white female who had onset on day 8 of a non-pruritic rash with erythematous macules and papules covering greater than 60 percent of her body surface area, with ulcers in her mouth and pharyngitis. But she was not withdrawn from the study, nor received systemic therapy and the duration of her rash was 7 days. Her quality of life was reported as being minimally affected.

[Slide]

This is the rash on the back of her legs, and a closeup of her shoulder.

[Slide]

Case five is a 39-year old white female with a history of hives to sulfa, who had onset on day 9 of a morbilliform urticarial eruptions with 40-60 percent of her body surface area involved, with erythema on the labial mucosa, and by labial I mean lips; this is not a genital lesion.

[Slide]

She was treated with acetaminophen only

and her rash lasted 30 days, and there was no quality of life assessment made.

[Slide]

Before I mention this case, I would like to mention briefly another case of a 21-year old female who had 5 percent of her body surface area with a pruritic rash, and this was the one individual who had associated fever and eosinophilia, with an eosinophil level of 0.62 with an upper limit of normal of 0.55. She had itchy eyes but no discrete mucosal lesions, and was treated with Allegra, with the duration lasting 8 days. But pictures of this rash are not available.

[Slide]

The last case is a 20-year old white female with no past medical history who had onset on day 6 of a pruritic rash with erythematous macules covering 20-40 percent of her body surface area. This rash lasted 4 days and no photographs of this rash were taken for unclear reasons, but the biopsy showed a linear deposition of IgM along the dermal basement membrane.

[Slide]

That is present here.

[Slide]

The other histopathologic findings have already been mentioned and in most cases mild, superficial perivascular infiltrates were seen, with moderate or deep infiltrates seen in 10 specimens; eosinophils noted in 10 specimens, with no particular pattern for CD4 cells or immunofluorescence. There were some faint deposits of IgM and/or C3 in dermal vessel lumina and in one case, which you just saw, along the basement membrane. But there was no evidence of vasculitis, bulla or necrosis.

[Slide]

I would like to move to study 344, part B now. I will not go over the randomization pattern because Dr. Shear already went over it. It was to determine whether or not there was cross-sensitization or subclinical sensitization. So, if you developed a rash to gemifloxacin in the first part you got either cipro. or placebo. If you didn't, you got either gemifloxacin again or placebo. Excluding the 027 center, you get a rash rate of 5.9 percent for individuals who received cipro. after having developed a rash from gemifloxacin.

[Slide]

These results really show us that there is a suggestion of a minor cross-sensitization with ciprofloxacin but it is not really conclusive data, nor can we really extrapolate about cross-sensitization with other quinolones. There is really no significant evidence of subclinical sensitization with gemifloxacin.

[Slide]

One thing I would like to mention before concluding is a brief literature review looking at the association of quinolones with severe cutaneous reactions. In a review by Roujeau et al., which I believe includes Dr. Stern, there was a multivariate crude relative rate developed. This was not just looking at quinolones but looking at all drugs in association with risk for development of Stevens-Johnson syndrome or toxic epidermal necrolysis. Crude relative rates were developed for a variety of drugs and, clearly, sulfonamides have a very high relative risk but for quinolones the relative risk was 10, with aminopenicillins at 6.7. A very recent literature review came up with 13 case reports of Stevens-Johnson or toxic epidermal necrolysis occurring secondary to a variety of fluoroquinolone agents.

[Slide]

In summary, the safety findings for gemifloxacin include a minor increase in mean QTc. There were some LFT elevations seen, particularly in those with liver disease or more comorbidity. With rash there was an increased overall incidence, with a large percentage of the body surface area involved and some severe rashes with mucus membrane involvement in study 344.

[Slide]

So, looking at the risk-benefit for the different indications being sought, for ABECB the considerations include the efficacy of the drug in the treatment of this condition; the length of therapy; the fact that it is a chronic condition often requiring recurrent therapy; what the rash rates would be in a population actually prescribed drug; the possible limitation of future quinolone availability in those who experience rash; and the fact that there were small increases in liver function tests and minor increases in mean QTc.

[Slide]

The risk-benefit considerations for community-acquired pneumonia include efficacy again in the treatment of this condition; the fact that

it is an oral therapy; what prescriber compliance would be with 7-day regimens. One thing not here, importantly, is the incidence of rash; the possible limitation of future quinolone availability in those who experience rash; possibly more hepatic effects in those with more comorbidity; and minor increases in mean QTc.

With that, I would like to take it over for conclusions to Dr. Edward Cox.

Summary

DR. COX: Just quick summary slides of a few of the items that have been discussed in the FDA presentation.

[Slide]

First you heard from Mr. Dionne about the microbiology review, and he noted and described some of the in vitro data and also some of the data from the animal models, and also provided some information about the pharmacokinetic indices to help put the MIC in context.

Then Dr. Alivisatos provided a discussion of the data for the community-acquired pneumonia studies. In this, she talked about duration of treatment of 7 days versus 7-14 days in light of the proposed dose duration of 7 days. She also

discussed the issue of severity of disease in the community-acquired pneumonia studies, and then provided some information and discussion of the data for isolates of Streptococcus pneumoniae from the clinical studies, including data on the resistant isolates for Streptococcus pneumoniae.

With regards to acute bacterial exacerbation of chronic bronchitis, Dr. Navarro provided an initial discussion of the principal studies and, in general, these studies support the efficacy in the treatment of acute bacterial exacerbation of chronic bronchitis. Then she also went on to talk about some of the statistical and clinical considerations for some of the other findings in the ABECB studies. She closed with a brief slide that talked about some of the population differences with regards to the antimicrobial usage data compared to the data from the clinical studies population.

[Slide]

Dr. Tierney provided information about gemifloxacin-associated rash and provided details about the rates, the characteristics of the rash and also some of the risk factors.

With regards to some of the remaining

questions, we have already had some discussion today and I expect we will have more but the issues of the risk for more serious dermatologic manifestations, the likelihood of cross-sensitization to other quinolones, and then some practical issues such as for patients who do develop a rash, the clinician's response to that and what the future antimicrobial options might be that would be available to such patients.

Then she talked about the hepatic safety profile of gemifloxacin and provided some information about perturbations in liver function tests in patients who receive doses in excess of the 320 mg daily dose, and provided some discussion about cardiac repolarization, and then provided some of the considerations in the overall risk-benefit profile for the indications of community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis.

So, just as a recap I will end there and turn it back over to the Chair.

Questions and Answers

DR. LEGGETT: Thank you. Are there any pressing questions that can't wait?

DR. BRADLEY: Just a very quick one. In

terms of the under 40 female age group that is at risk for the rash, does either the FDA or the sponsor have information on the incidence of rash by decade? Is this a straight line which has the highest incidence perhaps in the 20s or is it estrogen-related so that at the time of menopause the risk drops? So instead of a 40 cut-off, perhaps a 50-year old cut-off would be better? So, if there was some way to see by decade what the incidence of rash would be, it might be easier to put something into the labeling.

DR. TIERNEY: I have never seen a breakdown, other than under 40 or over 40. One thing that may help with that is the use of HRT. Over 40 HRT use does increase the risk. It might be related to that. But in terms of a breakdown by decade, I haven't seen data.

DR. LEGGETT: Dr. Patou is saying that that analysis has not been done. Any other questions?

[No response]

As far as I know, there is no open public hearing statement. So, why don't we reconvene here at 2:00 p.m.? We will answer some questions left over from the morning and then hear the charge to

the committee from Dr. Goldberger. Thank you.

[Whereupon, at 1:20 p.m., the proceedings were recessed for lunch, to resume at 2:00 p.m.]

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A F T E R N O O N P R O C E E D I N G S

DR. LEGGETT: This afternoon will be spent in discussing questions regarding the risks and benefits of gemifloxacin, but before that I would like to make sure that there is no one who showed up at the last minute, because of the snow, who wishes to speak at the open public forum.

[No response]

Before we get to hear the charge by Dr. Goldberger, were there any questions that the sponsor wanted to bring up in terms of the questions we had in terms of things that were left over from this morning? Anything that you wanted to say to address any of those?

DR. PATOU: The only piece of data that I think was requested was the confidence intervals from study 344. The FDA showed the confidence intervals from part B. f that addresses your question we are fine.

DR. LEGGETT: Thank you very much. Dr. Goldberger?

Charge to the Committee

DR. GOLDBERGER: I will try to make my comments brief. We have three questions. The first is, based on the data presented and in your

scientific and clinical opinion, do the benefits of gemifloxacin therapy outweigh the risks for the proposed indications of, (a) community-acquired pneumonia and, (b) acute bacterial exacerbation of chronic bronchitis?

It is worth noting that FDA agrees with the firm that efficacy has been demonstrated in both of those indications. I believe you have gotten the sense that there are probably some differences in exactly how we would describe the degree of efficacy, and we will come back to that in a second, but there is agreement that efficacy has been demonstrated.

In addition, activity in penicillin-resistant Streptococcus pneumoniae has been demonstrated. That is why we have not asked a specific question with regards to that. We believe how exactly that claim ought to be placed in product labeling, should you recommend approval for community-acquired pneumonia, is something that we will have a better handle on after discussion tomorrow, but we don't think actually there is enough doubt about that to really warrant a question.

As you discuss this, we want you to

include as part of your discussion the clinical and microbiological benefits of gemifloxacin. As I said before, there is agreement that the product is efficacious. As we all know, even though there is no statutory requirement that a product be better than what is out there or add value to what is out there in order to get approved, realistically when we look at the efficacy of the product, we need to do it in the context of the severity of the illnesses in question, the availability of alternative therapies and, in particular, what safety issues are posed by a product.

In this case, there has been some discussion obviously about some potential safety issues, and we will come back to those in a second. As a result, we feel it is important to talk about the efficacy and take into account these potential safety issues. So, one of the first steps is to talk some about the clinical and microbiologic benefits of gemifloxacin. As you know, the company has made a strong statement about the advantages from a microbiologic point of view in terms of enhanced activity against resistant pneumococci, and I think there is recognition that such organisms are important, and has tried to make the

case with regards to some benefits in some of agreed upon secondary endpoints in some of the trial. We think it is important, you know, to hear your perspectives on those different issues.

We also, obviously, think that it is important to talk about some of the safety issues. It is no accident that we have such a huge collection of dermatologists here today. I kept thinking if I had any dermatologic problem that I needed any advice on, this would be ideal.

[Laughter]

In any case, we want you to talk a little bit about the significance of the rash and, first of all, its frequency but, in addition, particularly as it relates to the likelihood of more severe dermatologic manifestations when the drug is prescribed to many more people and the likelihood of cross-sensitization to other fluoroquinolones. This is obviously a concern. Fluoroquinolone antimicrobials are important drugs for a wide range of infections, ranging from respiratory infections to severe systemic infections, urinary tract infections, etc. Getting a better feeling for these issues we think is essential in understanding how to proceed with this

product.

We would also like to have some discussion about the hepatic toxicity profile of the drug. You have heard analyses presented by the firm. You have heard some analyses presented by the FDA. As much as is possible, we would like to get some kind of consensus as to whether this is likely to pose a problem in actual use.

Question two is, if the answers to question 1(a) and/or 1(b) are yes, please discuss types of information that should be provided to physicians and patients. Please focus on elements outlined in question one, as well as any other issues you believe relevant. Please include as part of this discussion any caveats as to how and to whom the drug should be administered. For any risk communication or management strategies that may be appropriate, please comment on how practical and/or effective you think such strategies would actually be.

These are obviously issuers about putting statements in labeling about how long the product should be prescribed for, any cautions about if it doesn't appear to be working as well as about prescribing another course; what to do about

repeated prescribing and is that a concern? Perhaps even more to the point, what should somebody do if a rash develops? Should therapy be stopped? Can the drug ever be used again? What recommendations ought there be, if any, to patients for future use of fluoroquinolones, etc.?

The more information like that that could be put in labeling, the more helpful it is to physicians and patients to understand how a product like this can reasonably be used; the less confusion there is and, hopefully, the less likelihood of potentially more severe adverse events if, in fact, that is a risk; and concerns about an impact on future use of fluoroquinolones.

So, any useful comments you have about this, as well as any comments you may have regarding issues related to the efficacy, particular patient groups who would be felt to particularly benefit from the drug, etc., those are the kinds of things we would like to hear some comments about because a lot of those issues can potentially find their way into product labeling.

Finally question three, if the answers to 1(a) and/or 1(b) are no, please recommend what additional studies or information should be

obtained for both those indications, community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis.

We didn't specifically ask one other question that I just want to follow-up with, if you believe that the drug should be approved for one or both of these indications, we would also like to hear any comments you have about additional studies in the postmarketing period that you think might be helpful in better understanding both efficacy and/or safety issues. Those basically are my comments.

Committee Discussion

DR. LEGGETT: What I would like to have us try to do, given that charge, is to try to address these issues, starting off first of all, talking about the efficacy part of this in the first discussion session. If you want to say something about pneumonia or bronchitis, that is okay, we will try to link it up. Everybody, start thinking about what your answers are going to be because not only is it going to be yes/no at the end; it is going to be why yes or why no.

After we talk about the efficacy and, hopefully, if there are questions either the FDA c

the sponsor can elucidate them a little, then we will pass on to the safety part of it and have another discussion regarding the various safety aspects. During that part, for sure, I would like to hear at relevant time points what gastroenterologists, panel members and dermatologists and allergists have to say for the specific points involved.

Who would like to start either talking or asking a question, let's say, about what this drug is going to be for. Dr. O'Fallon?

DR. O'FALLON: In reading through the results of this, I was struck by the fact that no matter how sick the patients were, and there weren't all that many that were sick, really sick, and no matter what kind of bug they had, something on the order of 75, 80, 85 percent of them were improved or were considered successes. I can't see it in any package, what percentage of patients get better on no treatment at all, or placebo, or ineffective therapy in both of those diseases and I need to know.

DR. LEGGETT: Dr. Patterson, could you give us a little help with chronic bronchitis?

DR. PATTERSON: Well, based on earlier

discussions, the acute exacerbation of chronic bronchitis has been somewhat controversial as to whether antibiotics really make a difference in that disease. In fact, that is one of the diseases that we talked about in earlier discussions, that it might even be reasonable to do a placebo-controlled trial with that because it is not clear that antibiotics make a big difference.

* DR. LEGGETT: As a follow-up to that question, a statement was made, and I can't remember whether it was Dr. Mandell or who it was this morning, about efficacy was better in the gemifloxacin group in terms of either the time to relapse or hospitalization. I believe I asked Dr. Patou whether the trials were stratified according to steroid use, given the data that if you don't stratify for steroid use antibiotics make a difference in bronchitis case but if you do, they don't, at least in some studies.

DR. MANDELL: If I could just make a brief comment before addressing this, with ABECB in relationship to that question, and it is a good question, you really have to stratify according to severity. Unfortunately, there isn't a stratification scheme that everyone agrees to but

the Antonison is one approach. With that, the Antonison I or II, and Antonison I unfortunately means all three of the signs and symptoms, those patients do benefit. There have been a number of studies now that show quite clearly that those patients benefit. The Antonison III, which the mild, I don't think there is much argument, those patients may not benefit from antibiotics but the sicker ones definitely do.

[Slide]

On your question about steroids, this is the gemi. group, this is the clary. group and 25 percent of the patients and 24.6 percent of the patients. So, steroid use was even in the two arms.

DR. LEGGETT: That was within the last year. What about while they were being treated during that month or two afterwards? Do you have data on that? That looks like baseline data. I was wondering in terms of the actual treatment course.

DR. MANDELL: Do we have that data?

DR. LEGGETT: You can deal with that later. Mike?

DR. PROSCHAN: Yes, I wanted to get back

to the 7-14 day issue. Isn't it true that even the people who went to 14 days you still have outcome data at 7 days. So, why can't you look at all the 7 days, not just ones who only completed 7 but everyone? I mean, that eliminates the bias problem.

DR. LEGGETT: Does somebody want to tackle that?

DR. COX: I think the issue is that in the studies where there is a choice of 7 or 14 days it is not determined at the time of randomized whether somebody gets 7 or 14 days of therapy, but it is actually something that is determined on therapy.

DR. PROSCHAN: Right, I understand that but even if they go on to 14 days you still have their 7-day outcome. So, why can't you just look at everyone at 7 days, not just the ones who only went 7 days but the 7-day outcomes in everyone? Then you don't have the bias problem.

DR. ALBRECHT: I think in the evaluation of a trial of an infectious disease if we looked at a study where a patient received a certain duration of therapy, and then it was determined by some investigator criteria that that patient required additional therapy, i.e., up to 14 days, then our

assessment of that patient's progress at that 7-day time point would be that the patient was not successful because he or she required the additional 7 days. So, I think if we were to go back and do that, and I will defer to our statistical colleagues here but one of those analyses would have to be a sensitivity analysis assuming that all of those that received 14 days, in fact, would have been failures if they stopped at 7. That might actually bias the results the other way, making the success rate seem artificially lower than it really happened.

DR. PROSCHAN: So, there was not an outcome measured at 7 days? Is that what you are saying?

DR. COX: The primary outcome assessment would have been thereafter, and I think it is around day 21 with a window around it. That would have been the same for patients despite the course of therapy.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: Just to follow-up on that question, you could get safety data though after 7 days.

DR. TIERNEY: We did assess the safety for

all those patients, both on therapy and after therapy. So, if they had a safety problem on therapy that would still have been determined regardless whether it was 7 or 14 days.

DR. LEGGETT: Yes?

DR. HILTON: I have a different question on the efficacy. I wonder what the non-inferiority margin was. I see that some of the confidence intervals go down to as low as 10 percent inferiority and I wonder what was the cut point used to design the study and to think about non-inferiority.

DR. COX: For most of the studies the lower bound of the confidence interval is minus 10. There were some I think that were minus 15.

DR. ALIVISATOS: Some of the CAP studies were minus 15 and some of them were minus 10. In the sponsor's analysis, I think what they said, you know, post studies they tried to go to a delta of minus 10.

DR. HILTON: Okay. There was just a lot of focus on the mean rather than the lower bound and I wondered if attention had been paid to that.

DR. LEGGETT: Dr. Proschan?

DR. PROSCHAN: The reason I brought up

that earlier question is that I am not sure the FDA would agree that efficacy has been shown based on, you know, if you only consider study 11 as the primary study and the others as supportive, then one, namely 12, is not supportive. I mean, it is supportive of the opposite; 49 is supportive. So, I am not sure that it is true that the FDA would concede efficacy if you take the point of view that only study 11 is really the primary valid study.

DR. COX: Can you just restate the last part of your question there?

DR. PROSCHAN: Yes. I mean, the FDA's position, as I understand it, is that study 11 is really the only valid study of a 7-day course because the others have these biases. Then, the others are supposed to be sort of supportive. While one of them looks quite supportive, another one looks supportive of the opposite, namely that the competitor is better. I don't know whether it suffices to show that, you know, in at least one trial it is better or what the level of evidence required is. This is page 69. In particular, I am just looking at the ITT population but a similar pattern is in the PP population. Study number 49 is certainly supportive but study 12 is going the

other way.

DR. COX: For study 12, if memory serves me correctly, the lower bound of the confidence interval was minus 10.2. In some of the discussions earlier on during the drug development there was discussion of a confidence interval that would even be beyond the 10 percent, during the time when the NDA was being discussed. So, you know, I believe that lower bound, 10.2, is just beyond the 10 percent.

DR. LEGGETT: Go ahead, Mark.

DR. GOLDBERGER: It is also worth keeping in mind that one needs to put the issue of the confidence intervals sort of in a broader perspective. Clearly meeting a previously agreed upon confidence interval is the easiest way to get an approval absent any unusual safety or other issue. The fact that you may in one of the studies be just over the confidence interval doesn't, of itself, mean that study does not indicate that the drug had activity. I don't think, looking at the data, we would conclude that gemifloxacin is without activity perhaps in community-acquired pneumonia.

However, it raises the broader concerns

when we are then obliged to look at the overall activity as it has been demonstrated in clinical trials, and then link that to some of the potential safety issues that we need to talk about as well. That is where being on the borderline with some of the confidence intervals may prove to be, you know, a little bit more problematic.

DR. LEGGETT: I have a couple of questions regarding kinetics and the mechanism of action. Maybe someone can help me from the sponsor.

Much mention was made of the dual targets with the relative affinity being the same. When I look at the actual data, which in the FDA is on page 20, Table 14 and Table 15, to me, when I look at the difference between the wild type and then either the Par or the GyrA or the dual resistant mutants, to me it looks like gemi. and moxi. certainly aver very similar in terms of their fold range rise for those two things. I am wondering how much of a qualitative difference there really is between moxi. and gemi., rather than sort of just a purely quantitative change and calling 4-fold not significant and 8-fold significant and vice versa. When I look at the rat data I see that when the MIC becomes 0.25 or so the CFU declined in

presumably the rat pneumonia model, really dropped off sharply for gemi. At least for those three strains, basically moxi. and gemi. did pretty much the same. I was wondering whether you could sort of overall comment about those issues.

Not to beat a dead horse but the breakpoints will obviously play a big role in terms of how things are marketed, and I would hate to see a breakpoint pushed high, as was done with levo., which makes things there still labeled as intermediate or even susceptible, not being clinically susceptible.

DR. PATOU: I would like to ask Dr. Steve Brown to comment on that question with particular reference to the table you referred to.

DR. BROWN: Could I have slide M63, please?

[Slide]

This is the sponsor's version of essentially the same table as the one that you referenced. Yes, indeed, there are some marked similarities between gemifloxacin and moxifloxacin in the rat lung model.

There are a couple of things that I would point out to you, one of which you have already

observed. There is marked similarity between gemifloxacin and moxifloxacin in the majority of the cases. However, there are three distinct issues here. In this instance, in which case there is a statistically significant difference between both gemifloxacin and moxifloxacin or gatifloxacin, in this particular instance there is a second step mutation and there is a statistical difference between gemifloxacin and moxifloxacin. Finally, in this case there was a statistically significant difference between gemifloxacin and gatifloxacin.

Yes, there are some similarities there. That cannot be denied. However, there are no instances in which moxifloxacin is more active than gemifloxacin. We have those two out of eight instances where gemifloxacin is slightly more active than moxifloxacin.

In a semi-related matter, if I could call up FDA slide 10, please?

[Slide]

This was presented earlier by the FDA. These are looking at the 44 bad bugs. These are 44 strains of Strep. pneumoniae with second step mutations. Even using the FDA's very conservative breakpoint of 0.125 I think that you can visually

see that there is quite a difference between gemifloxacin and moxifloxacin in terms of the in vitro activity. This is also very clearly reflected in the MIC-90.

What we did during the lunch break was go back to the line listing and look at these individual paired data, pairing up gemifloxacin results with moxifloxacin results. Subjecting those paired data to statistical analysis using the Nieman's test for binary paired data on these 44 strains, we found that there were 25 strains that were resistant to gemifloxacin--these strains. Of those 25 strains, and you cannot appreciate it from this slide; you have to look at the paired data. Of those 25 strains, none of them was susceptible to moxifloxacin. Looking at 11 of these 19 strains that were susceptible to gemifloxacin, 8 of those were also susceptible to moxifloxacin.

So, when you do this paired statistical analysis, you get a p value of 0.00098. So, the differences between gemifloxacin and moxifloxacin are, indeed, statistically significant. It was reflected in two of the eight rat lung models and reflected in the in vitro MICs quite clearly.

DR. PATOU: I think Dr. Klugman could

address the affinity question that you asked about the binding at the two sites.

DR. KLUGMAN: Keith Klugman, from Emory University. I think the issue of affinity does go more towards direct measurement of MIC. So, the drug affinities of gemi. are likely to be significantly higher and that is what has led to the lower MIC.

I think that the context of this is important because I have been listening to the discussion and, clearly, it is a great concern to me that we need to consider where one goes beyond the fluoroquinolones for these indications. I think that the data we saw of the rat lung model got me thinking that for those strains where there really was no good efficacy of either agent, what is left?

So, one of the arguments I would make in favor of this agent would be perhaps a lower propensity, because of this higher affinity for selection of resistant mutants so that one could come to an analysis of a condition like acute exacerbations of chronic bronchitis where you have a need for multiple rounds of therapy. So, at the moment my feeling is that clinical consensus is

that once you have had a fluoroquinolone, any fluoroquinolone, you are at risk for subsequent resistant disease. In fact, many guidelines are now going to say that if you have had any fluoroquinolone for AECB you shouldn't have any other fluoroquinolone for at least four months. The argument then would be in favor of using perhaps the most active agent so you wouldn't have this development of resistance.

DR. LEGGETT: A quick follow-up, what is the reason for the much higher MICs for gram negatives if this really is a dual target and the MIC is the marker of choice?

DR. KLUGMAN: I think it is a question of the affinity of the enzyme; it is different in different organisms. So, we are really talking about gram positive topoisomerase. There is a greater affinity for this drug for that particular topoisomerase and less so for the gram negatives.

DR. LEGGETT: Has anybody looked at what happens to the gram negative flora while we are taking this drug to treat our respiratory flora?

DR. KLUGMAN: That is a good question and, clearly, there is a quid pro quo on both sides of this equation. Clearly, if you use less active

fluoroquinolones against gram positives you are in danger of selecting resistance, say, in the pneumococcus. You could equally argue that using any of these agents may be less useful than using, say, ciprofloxacin against the gram negatives. So, you have a trade-off on either side of the equation, in my view.

DR. LEGGETT: Thank you. Alan?

DR. CROSS: I was interested in Dr. Low's data where you showed that if you had a mutation in both the ParC and GyrA with the gemi. you still had an MIC of less than 1; it was 0.25. I was just wondering, first of all, if it is known how these isolates are killed and, second of all, is it known whether or not gemifloxacin has any other antibacterial effects, other than on the killing, much like clindamycin affects the amount of capsule in bacteroides, for example?

DR. LOW: To answer your second question first, there is no other evidence that it has other beneficial effects with regard to reducing virulence or decrease protein or toxin reduction. I guess I wouldn't be surprised that really it just affects DNA replication.

Why is this drug still able, even in the

face of mutations, to bind to these targets? It is called a cleavable complex. So, the way it works is that you literally have the topoisomerase enzyme wrapped around the DNA which allows it to open up and so you can replicate. The fluoroquinolone comes in and locks that together so it can't dissociate and it causes loose ends of the DNA which kills the bacteria. Presumably, it is the structure that allows--you can literally see it on the molecule where the mutations occur how it affects binding affinity. So, you get a mutation and that mutation may disproportionately affect levofloxacin but gemifloxacin is still able to bind to and hold these two together and be bacteriocidal, as I showed in that one killing slide. So, it is just the structure of the compound.

DR. LEGGETT: Thank you. Could I hear some comments perhaps from the committee members about their feelings about the number of severe community-acquired pneumonias that were in the trials, or lack thereof? Dr. O'Fallon, you are really good for this one.

DR. O'FALLON: I was trying to find the data and I just did. I am looking at the FDA

packet, page 10. Take a look at the numbers, 13 in one group; 11 in another; 31 and 26, 34, 30. There aren't very many in any of the treatment groups that were classified as having severe disease. So, those are small sample sizes.

One of the things that concerned me is the response rates. They are still up in the 85 and 95 range for the most part. You know, if there is supposed to be more severe disease--this is true for the comparators as well--that is what makes me wonder whether any treatment will do. So, it really doesn't matter what you treat them with, they are going to get better, most of the people. If that is true, then is this evidence for the activity of any drug? If the underlying disease is going to basically get well no matter what you give them, then is this evidence for any of them being active?

DR. LEGGETT: I guess one question that people tried to address was the difference in mortality between in the Fine study either in the validated or the initial modeling of the difference between the two groups.

Going through here in my reading, I only saw mention of six intubated patients. Is that

correct? And, all six were considered failures? Or, you know, was I just falling asleep?

DR. ALIVISATOS: At the time of enrollment there were no patients that were intubated or on pressors, things like that. During the study, during the course of treatment six patients altogether did ultimately--actually, there were two that were intubated, two that required pressors, and those were all failures.

DR. LEGGETT: But not big numbers.

DR. ALIVISATOS: No.

DR. LEGGETT: Dr. Poretz?

DR. PORETZ: Those patients who were seriously ill who were intubated were maintained on gemifloxacin during that period of time?

DR. COX: They were put on alternative therapy.

DR. PORETZ: Because in actuality, someone who is admitted to the hospital with a Fine I or IV even, in all honesty, is going to be put on parenteral antibiotics for practical reasons, whether it be insurance coverage or whatever. Many people won't pay for putting a patient in a hospital on oral medications. So, the sicker people will have to be on parenteral medications.

DR. LEGGETT: And I would be worried about their absorption anyway.

DR. PORETZ: Yes.

DR. LEGGETT: Barth?

DR. RELLER: There are several pieces of data that support less severely ill, not only the Fine scores, but the overall mortality and also the proportion of bacteremic patients, which is substantially less than most studies. So, I think that there are real limitations on excessive exuberance about the efficacy of this drug in CAP. Clearly, the sponsor's request for inclusion of Staphylococcus aureus in particular but even Haemophilus influenzae and Moraxella catarrhalis--over and above the majority of information is about Streptococcus pneumoniae. I just don't see the numbers and certainly I don't see any numbers where one is absolutely sure that patients have those entities, apart from the pneumococcus, and even with the pneumococcus the number of bacteremic cases is less than 50.

DR. LEGGETT: Can we pass on to the question of efficacy against multi-drug resistant pneumococci since you brought up pneumococci? Anybody want to give it an opening volley?

To follow up on what Dr. Reller said, when I looked at the bacteremic, I think it was 37 of the 48 bacteremic cases were pneumococcus and 16 of the 17 bacteremic pneumococci did respond but it is still smaller numbers than what we saw in the others.

DR. RELLER: I was thinking about the query earlier about how many are required to be certain. I recall at multiple meetings ago when ofloxacin was presented there were over 100 bacteremic cases of pneumococcal pneumonia. People are pretty certain that they had pneumococcal pneumonia when the blood culture is positive, which leads to an additional question that there was not the time to ask earlier. Were there any other attempts, given the limitations of sputum cultures in the confirmation of the diagnosis of pneumococcal pneumonia since these are all adult patients and we don't have the difficulties of specificity with children, was pneumococcal antigen assessed in the urine of these patients? As published from New Zealand it is actually a reasonable test to augment the objectivity beyond the positive blood cultures where, you know, all of us would agree, as Dr. Brown was mentioning

earlier, chest infiltrate, sputum production at least after being hydrated and a positive blood culture for the pneumococcus was certainly what we had, and a relatively small number of those with efficacy with this or any other compound, it seems to me, is a lot more powerful than large numbers of questionable severity by several accounts with a relatively small number of bacteremic patients. So, are there any data on pneumococcal urinary antigen detection in any of these studies?

DR. ALIVISATOS: Two of the studies, the open study which is still ongoing, number 287 which is an enrichment study, one of the inclusion criteria is to have a positive urine pneumococcal antigen. Also, in study 011, which again was sort of an enrichment study, I mean, they tried again to enroll people that probably had pneumococcal disease and you had to have gram positive cocci on the sputum gram stain and, in other words, there were some clinical criteria there.

Just to clarify first, for the 37 of the 48 bacteremic patients that had Strep. pneumo. bacteremia, the success rate for the group of patients that received treatment for greater than 7 days was 95 percent. The success rate for the

people who received less than 7 days was 94 percent, even though you shouldn't look at it like that.

DR. LEGGETT: I had a little question regarding what was stated a couple of times, first by Dr. Mandell and then later by the FDA and then what I saw in our FDA packet on page 57. On page 57, I don't want to fault anybody's grammar but I couldn't understand what you were saying. Were four out of four cipro. resistant pneumococci strains treated successfully? Or, how many were "others" were associated with clinical failure? I got lost. I think Dr. Mandell, if I heard him right, said 26 of 28 cipro. resistant strains were cured and I am having trouble with the numbers.

DR. ALIVISATOS: There were four patients with cipro. isolates that had an MIC of greater than or equal to 4, which is considered resistant. The rest were intermediate.

DR. LEGGETT: So, there were 22 intermediate and four resistant. Did you want to say something, John?

DR. BRADLEY: It has to do with emergence of resistance because as quinolones are used more, particularly if there is ever a pediatric approval

for one of the quinolones, we may see more resistance. So, looking to the future and knowing in vitro the activity of the drug and the types of mutations that you need in pneumococci in order to develop resistance, in gram negative pneumonias there have been pharmacodynamic models which look at an AUC to MIC. If you get below an AUC to MIC of 100, the likelihood of emergency of resistance goes up dramatically. If you are above 100, then you tend not to get any resistant organisms. I am wondering if the company has done pharmacodynamic modeling perhaps in the rat, because you certainly don't have these same kinds of data in people, on what AUC to MIC ratio you would require to prevent emergence of resistant organisms.

DR. LEGGETT: To follow-up with that, do you have kinetics and then a Monte Carlo simulation of patients at all?

DR. BRADLEY: This would just be supportive data to show that the mutational resistance is very low, and if you have a certain drug exposure at 320 mg a day that you would be unlikely, given the current MIC-90, to develop resistance, and then compare that with other agents.

DR. PATOU: We haven't done the specific AUC to MIC modeling that you described on gram negative organisms, but I think that Dr. Jacobs has worked in this area and might have a comment to say on this.

DR. JACOBS: I think I can give you a general answer to that. There is some data showing that you prevent resistant mutants at an AUC to MIC ratio of free drug of 100 or greater, whereas for efficacy, especially for gram positives, you probably need 25-30 as a lower number.

There is also some controversy as to whether 100 is needed for gram negatives and 30 for gram positives, or whether you need 100 for immunocompromised patients and only 25-30 for immunocompetent patients. I think a lot of that still needs to be dissected out as to which factors come into it, but I think, to me, the bottom line for gemifloxacin is, whichever parameter you look at, against either susceptible or quinolone-resistant Strep. pneumo., it has the highest parameter, higher than any other drug including ofloxacin.

DR. LEGGETT: Although I would hasten to add that 97-128 is no different than 96 in terms of

these numbers because of the huge difference that the MIC makes. That is where most of your pharmacodynamic variability is. So, going from 0.125 to 0.25 shoots it in the foot, for instance.

DR. JACOBS: No, if you are just looking at pure ratios, if you are looking at ACU to MIC ratio gemifloxacin is about 20 percent higher than moxifloxacin. I think that is what you were referring to. But if you look at peak to MIC ratio for both susceptible and resistant strains you see an even bigger difference. For susceptible pneumococci gemifloxacin is over twice that of moxifloxacin for free drug. When you look at resistant strains the ratio increases to five-fold. The peak to MIC ratio for ofloxacin, based on MIC-90 of quinolone-resistant strains is 0.55, whereas for gemifloxacin it is 2.6.

DR. LEGGETT: At least this year.

DR. JACOBS: Sure, but as the MICs go up for one, they are going to go up for the other.

DR. LEGGETT: Sure. Just couldn't let you off the hook that easily!

If we have beaten community-acquired pneumonia to death, could somebody make some comments about the secondary endpoint issues that

were brought up with the chronic bronchitis issues? Do you keep people out of the hospital? Is there a longer time to relapse and those sort of things? Anybody care to make any comments about the efficacy data as far as that is concerned?

DR. PROSCHAN: Yes, I, for one, don't believe the hospitalization results. I am trying to find that picture in the FDA document that shows the log rank curve.

DR. LEGGETT: The hazards ratio?

DR. PROSCHAN: Yes, page 67. To me, we often go by log rank and I don't see much of a difference here, a p value of 0.16. You know, there also do seem to be some pretty big jumps near about 10 days, and I don't know whether that is some kind of important cut point as far as insurance is concerned but it looks like something might be happening there. So, taking all that into account, I tend to discount that particular claim of benefit.

DR. LEGGETT: I might only add in terms of the time to the next infection or rehospitalization or relapse there is some data apropos of this with steroids in the last couple of years, in The New England Journal of Medicine, looking at steroids

and chronic bronchitis exacerbations and the time that you can prevent rehospitalizations, reinfections and that, of course, diminishes over time so that by the time you are out to six months or longer there is really no difference. It is a very short time frame. So, I would hate to carry out the data too far in terms of a five-day course of they when giving influence on relapse rates two, three and four months later. Don?

DR. PORETZ: The slide was shown a little while ago about the number of drugs approved by the FDA for ABECB. There are at least half a dozen cephalosporins on the market, a bunch of quinolones on the market, macrolides on the market. The fact is there are so many drugs, I can't believe this is any better or any worse than any of those other drugs that have already been approved by the FDA for bronchitis.

DR. LEGGETT: So, you are suggesting we jump from efficacy to toxicity?

DR. PORETZ: Yes.

DR. LEGGETT: Okay. Why don't we bite into the big one first, rash? Oh, sorry, Barth?

DR. RELLER: I would like to come back to Dr. O'Fallon's earlier query. Since these patients

with acute exacerbations of chronic bronchitis were not stratified before entry and, by my reading, better than 95 percent of them or, let's put it another way, fewer than 5 percent of them were in category III, the more severe, in previous discussions of the committee I think legitimate queries have been raised as to not only being ethical but perhaps obligatory to have placebo-controlled trials to assess the efficacy in acute exacerbations of chronic bronchitis. Particularly when better than 95 percent of these patients are not in the severe category, I am not certain now to interpret this information, the bacteriologic data. There are actually as many or more with some of the putative agents that most people don't think cause, or are not important in acute exacerbations of chronic bronchitis, namely Staphylococcus aureus, is they are all for Streptococcus pneumoniae.

So, what is proposed is a leading pathogen and we are going to diminish resistance and we are going to have a great effect because of the efficacy of this compound in vitro against Streptococcus pneumoniae. When you look at the microbiology data with these milder cases of acute

exacerbations of chronic bronchitis the numbers simply aren't there.

Now, does it work as well as the other compounds? It probably does. How it works versus placebo in these patients I would like to know because you get into the safety issue in terms of not does it work as well as other comparators but, given the numbers of patients, does it work sufficiently well over placebo to encounter the risk? One could say, well, the rashes are mostly in the younger patients who don't have acute exacerbations of chronic bronchitis. On the other hand, in the touted 344 study, and it was impressive, there were all of these challenges that people had rash and didn't have rash with ciprofloxacin but, unless I missed it, I didn't see the gemifloxacin rash and gemifloxacin again. Given the frequency of use of agents and repeated, recommendations not withstanding of not repeating any fluoroquinolone within X period of time, what is the reality of people getting gemifloxacin again? I think there are a lot of questions with acute exacerbation in chronic bronchitis in the data presented to us.

DR. LEGGETT: I would like to add to that.

From my own real-world perspective, the fact that it is approved for AECB means that it is automatically used in acute bronchitis and the numbers there are overwhelmingly young. Also, in community-acquired pneumonia if you look at the Fine data, 67 percent of those people are under 40 and they are outpatients.

DR. RELLER: Actually, in the six or so patients that were listed as having severe reactions, most of them admittedly overseas, I, maybe incorrectly, assumed that EBS, which was the diagnosis, was acute bacterial bronchitis. Maybe I didn't get that straight. Guideline after guideline, you know, from IDSA has come out that that is not an entity that warrants antimicrobial therapy.

DR. LEGGETT: Jan?

DR. PATTERSON: I have a comment but it is actually not related to that. It is about the multi-drug resistant indication that you brought up before.

DR. LEGGETT: Sure. Oh, go ahead.

DR. PATOU: Just to provide clarification for the committee. Just two quick points. One is that all of the AECB studies that were conducted

were studied according to the existing guidelines for the assessments of acute exacerbation of chronic bronchitis. They were conducted over a three- or four-year period and they were conducted to the standard that is expected of a sponsor for the assessment of the efficacy of the drug in AECB, and we were not asked to include a placebo in those studies.

The second point is that the definition of AECB in these studies did meet the accepted criteria for AECB. If there is a reference on a slide, and I think it may have been a safety slide, to EBS that was referring to a patient in an acute bacterial sinusitis study, not an AECB study.

DR. LEGGETT: Dr. Powers?

DR. POWERS: I want to make a comment about where we are going with AECB trials. It is true that gemifloxacin's development program was long before we brought up some of these issues and we would never hold them to something that we had, you know, discussed just recently. But in November there was a workshop being co-sponsored by the IDSA, the pharmaceutical industry and the FDA where we discussed just these issues of acute exacerbations of chronic bronchitis trials, and

there was a consensus among the representatives there that placebo-controlled trials would be something that folks would want to see, given this idea that the placebo rate in patients treated in that disease would be very high. Again, that is not something we would hold a development program that is already completed to, but to say that that is the current guidance I don't think is true anymore and, from this point forward, we would be really looking towards more placebo-controlled trials.

DR. LEGGETT: Jan?

DR. PATTERSON: Related to the multi-drug resistance issue that you brought up before, and we have discussed this before, I think, as Dr. Powers was proposing, the multi-drug resistance indication makes more sense, especially, as he pointed out, the data is accumulating that really for isolates that have penicillin MICs less than 4 there doesn't seen to be a significant difference in clinical outcome, and actually macrolide resistance is more important than what we are now calling penicillin resistance on the label. That may change when we have more isolates with MICs greater than 4. But rather than, you know, adding on drug after drug to

penicillin resistance, second generation cephalosporin resistance, macrolide resistance, perhaps we should say multi-drug resistance and define that as at least three classes of drugs.

DR. LEGGETT: So, in AECB we are going to go against placebo. If there is more toxicity and they don't have a multi-drug resistant pneumococcus they are not going to get--it doesn't make sense. It is getting complicated.

Can we pass on to toxicity issues? Perhaps the first question would be rash. I was rather intrigued that some people in 344 who developed rash the first time around did not get the second, especially from your comments earlier, Dr. Bigby, about if someone had a cephalosporin rash that you wouldn't want to give it again. Is there something fundamentally different about a fluoroquinolone rash that you or anybody else knows?

DR. BIGBY: I guess the only thing that I would say about this is that I was surprised by this result, the gemifloxacin rash and then ciprofloxacin and the point estimate rate was 5.6. I would just point out that the N is small and that doesn't exclude the possibility of a reaction rate

as high as 9 patients out of 100.

DR. LEGGETT: Dr. Rodvold?

DR. RODVOLD: Would you anticipate it would be different in patients versus a volunteer study? In patients do you think it would be higher?

DR. BIGBY: There is no way to know.

DR. LEGGETT: Dr. Epps, anything to add to that in terms of your interpretation of rashes?

DR. EPPS: I guess just a general comments. I certainly appreciate the company's work and the additional study that was performed. I was very happy to see pathology and histopathology, and it was very reassuring that there was no vasculitis. There didn't seem to be immune complex diseases. That is very reassuring.

I was impressed by their data on MICs, although some people don't think it maybe as pertinent but I thought it was interesting. What I guess concerns me is the high incidence of eruptions in people who were normal. In women under 40, 31 percent had eruptions. Now, if they were ill I have no idea what the rash rate would be but 31 percent is quite high. The mean onset was 9 days, which is beyond the 7 days and it certainly

lasted at least a week in over half the cases.

So, certainly, you know, one would wonder what it was about women below 40, what hormonal influences were there. There was discussion about oral contraceptives. What about people who use Norplan? What about people who use Depo-Provera, older women who are on hormone replacement therapy? There seems to be some kind of a theme there. Whether it needs more investigation I don't know but the rate is very concerning to me. Certainly, you know, I would consider something different if it were a woman under 40. So, maybe some adjustments could be made for that.

DR. LEGGETT: Wear an anti-drug bracelet?

[Laughter]

Dr. Drake?

DR. DRAKE: Well, I too want to compliment the sponsor because the 344 study is terrific in dermatology. It is long needed and we need more of it so we can start to sort some of this out.

Maybe I am not reactionary enough. It seems to me that we have other drugs that give us these kind of non-specific rashes. In absence of vasculitis and in absence of immune complex disease, gee, if I see a rash and I don't know what

it is I get a biopsy and get it frozen and kind of find out what is going on. But in the absence of those things, it is not uncommon--and I think it is a standard in dermatology--it is not uncommon to what we call treat through some of the rashes. It is particularly true for some of the antifungals. You just treat right on through. People get these rashes and you treat them and keep on going and pretty soon the rash resolves all by itself anyway.

Now, that doesn't mean that you are not prudent. It doesn't mean that you don't think about what is underlying the rash and exactly what the pathophysiology is. But, in fact, I am not terribly alarmed by this. If you have a good drug that might treat a patient who might otherwise not be treatable by something else, in other words, if this is a nice alternative or nice addition to the therapeutic armamentarium, then I wouldn't let the rash preclude me from using it or considering using it.

I do think that one can address this issue by looking at the labeling and a Phase IV study to further separate it out a little bit. In all honesty, you are not going to get much answer on the rashes in clinical studies. The power is just

too low. You are just simply not going to have it. You are going to have to get it out in the real-world use and then follow them and monitor the rashes and monitor the patients and see what happens. So, I think as a practical matter, if that is the only limiting factor it makes more sense to get it out there and get it in real-world use and then monitor it in Phase IV and tease it out at that time.

DR. LEGGETT: Yes, go ahead, Dr. Bigby.

DR. BIGBY: I believe that gemifloxacin has been licensed in several countries in Europe and I wonder whether there is any postmarketing surveillance data vis-a-vis its frequency of producing rashes and the duration at which it is used in the countries where it has already been licensed.

DR. LEGGETT: They are shaking their head, no.

DR. PATOU: I mean, the drug has not been launched anywhere at this point in time.

DR. LEGGETT: Could I get an opinion from Dr. Adkinson and the three dermatologists about if you get this rash, is it going to become anything different the second, the third or the fourth time

around? If that is the case, to me, the clinical paradigm in the United States is if somebody comes in and you have seen their penicillin rash, they don't get penicillin again. If I have seen their fluoroquinolone or cipro. rash, I don't give it again. Could the committee get your opinion about that?

DR. ADKINSON: Could I put that off for just a second and just comment more generally about the rash issue as I see it?

If you just look at the clinical trial data, the rate of this apparently benign, late occurring maculopapular rash is about 3.6 percent versus 1.1 percent in the comparator group. If you look even more specifically at those that were considered by the investigator to be probably drug related, the rate of rash is 2.3 percent compared to 0.6 percent. So, there is a drug specific excess rate for sure, but I don't think that would have garnished very much attention except for this demographic factor of a very high prominence rate of this rash in young women. It is young as opposed to women and it seems to be the important factor.

The rate of reaction is going to be a

little more in the chronic bronchitis, about 1.5 percent, and somewhat higher in CAP, about 4.7 percent because of the demographic factors, and the fact that bronchitis is a disease of older men I guess and community-acquired pneumonia has a much larger fraction of younger women. So, we are in a range where other antimicrobial drug preparations commonly induce rash rates in this area.

So, for me the issue is, does this rash portend something about this drug that is different from other similar appearing rashes that occur with comparable frequency, putting aside for a moment this issue of gender and age risk factors? From what I have heard today, I am reassured I think, especially by this very large 344 study, that this rash behaves very much like the diamino-penicillin rashes that we have become familiar with and that we know occur with high frequency and that, with appropriate co-factors, can approach 100 percent in cases, as you know, where there is coincident infection with EB virus or even other proven viral infections, or the co-administration of allopurinol.

So, high rates of rashes don't necessarily portend a substantially worrisome clinical outcome,

it seems to me, judging from what we have learned to tolerate and to deal with clinically in the case of the diamino-penicillins.

Coupled with that, I am reluctant to make too much of the incidence of rash in study 344. I mean, everybody is a bit wowed by this 31 percent rash rate in the participants in this study, but part of this very high rash rate is due to the surveillance factor that Dr. Bigby talked about today. The patient population chosen for study were young females who were taking the drug for ten days or more. If you go back and look at the clinical trial data, the rate of rash expected or observed in that group was 15 percent. Once you set up a prospective study aimed at looking at rash, the rash rate goes from 15 percent to 32 percent.

Since we don't have any other studies that I am aware of, of this type of large-scale, prospective study of rash from drugs, this may not be as unique or as unusual as we might otherwise, just looking at the numbers on the surface of things, believe. It has taken me a while to sort of see that, but to me, that helps to assuage the numbers a bit with the fact that we don't really

have comparison groups. I don't know how we interpret these numbers and then I have to fall back to the issue of the clinical consequences.

As much as I have tried to, you know, search the database here and probe our presenters today about evidence for systemic findings associated with these rashes, I am not convinced that we really have anything that is above the background level of noise that we would see in a clinical trial of this type. There is certainly no red flag or worrisome data here, in my mind, to suggest that these rashes are going to turn into something to be clinically very worrisome if the drug is given to a much larger number of patients.

To go back to your question, Dr. Leggett, I don't know the answer to that question but you are absolutely right in making the observation that once a patient is pegged as having nominally a hypersensitivity reaction to a drug, the usual clinical course is that that drug is withheld for the duration of that patient's life unless a particular physician has some belief that allows him to readminister or rechallenge patients or to move beyond the standard of practice, which is to withhold drugs generally that have caused problems

in the past under the presumption that they are going to be a problem again.

DR. LEGGETT: Do the three dermatologists concur in general lines with that statement?

DR. BIGBY: Which statement?

[Laughter]

DR. LEGGETT: The most recent one, treating again or withholding treatment.

DR. BIGBY: I would agree with that, yes.

DR. DRAKE: I don't. As I said, in dermatology, frankly, we haven't done a very good job of sorting all this out and I think we are pretty good doctors so I don't want to disparage my specialty. I just think this is an area that hasn't perhaps gotten as much attention as it deserves.

I would like to compliment the FDA for putting this issue on the table. This is really an important issue because people should not be labeled--I was labeled allergic to penicillin as a kid because of a slight ampicillin rash. I mean, it is ridiculous; I am not allergic to penicillin. I think people miss out on good things and I think this reaction of if you have ever had any kind of a thing on your skin we don't ever give it again is

probably inaccurate.

I think we have to be more thoughtful and that is why I say I cheat. I tend to get biopsies and get frozen sections. I want to know what is going on underneath the skin and then make a better educated decision. But I don't think you can say, just because you had some kind of a "rash" without defining that, that you can tell a patient they can't ever have that drug or that category of drug again. If the FDA does approve this, I think it begs the question of sponsors trying to educate physicians on what we can do and what we can't do, and what is a reasonable approach to this type of patient.

DR. LEGGETT: Dr. Bigby? Everybody is raising their hands. Folks who want to jump in on this, please raise your hand again.

DR. BIGBY: I just want to say if a patient develops, while they are taking a drug, a drug exanthem and you don't have another explanation for it, I think it would be a big mistake to give it back to them.

DR. LEGGETT: Dr. Epps, can we say that this is maybe not universally shared on either side? Dr. Adkinson?

DR. ADKINSON: I just wanted to call our attention to the fact that the only data that I am aware of that deals with this directly were nice studies done in the late 1960s and early '70s with amoxicillin in which patients who had late-appearing maculopapular rashes, very similar to the ones we are talking about today, were intentionally either treated through or rechallenged. Two of these studies were pediatric populations. They showed that the rate of rash with the first exposure was, I think in this case, about 10 or 12 percent. They took reactors and re-exposed them to the same drug again and got another 10 or 12 percent reaction.

So, when it has been done, in a very limited way admittedly, and it involves the presumption that the rash we are dealing with today is in some ways similar, other than its clinical phenotype which is very similar I think to the amoxicillin rash, it gives us some suggestion that clinical practice here may be very conservative with regard to what is possible if one is willing to do provocational challenges and gather the data to support readministration.

DR. LEGGETT: Dr. Bigby?

DR. BIGBY: The best rechallenge data actually was done by a group in Scandinavia. The lead author is Cal Pinin. They did rechallenge studies to exanthems to fixed drug eruptions, and I think that the rate of sort of identification of culprit drugs is actually much higher than 10 percent.

DR. LEGGETT: Dr. Wald?

DR. WALD: I think that this study provided the data about rechallenge so the gemi. rash-gemi. was 2.4 percent, substantially less than 31 percent the first go around. I think this is really such reassuring data that, in fact, we should tell people that if a patient gets a rash it is not a contraindication specifically with this drug to get the drug again.

DR. TIERNEY: Dr. Leggett, can I just clarify? Dr. Wald, no one who received gemifloxacin and developed a rash got gemifloxacin again. Those are people who had not developed a rash to gemifloxacin and then got gemi., they had a 2.4 percent rash.

DR. LEGGETT: Yes, go ahead.

DR. SHEAR: That is not completely true. In 344 nobody was supposed to get gemifloxacin

again but two individuals did get gemifloxacin again, as was found out when the mask was broken. One received just one dose I think and the other actually got a complete dose, and neither had a rash.

DR. BIGBY: But an N of two--

DR. SHEAR: No, no, I am just telling you--

DR. BIGBY: Why bring that up then?

DR. SHEAR: I showed you the data which is quite convincing--

DR. BIGBY: Yes, but it is zero out of two. What does it tell you? The reaction rate could be as high as two-thirds.

DR. SHEAR: It tells you less than the four percent that I showed you here but that is more than no other data for any other drug.

DR. LEGGETT: Thank you. Dr. Rodvold?

DR. RODVOLD: In the aspect that you would go to all kinds of patients that could have pneumonia, is there anyone that you would say don't give the drug to because of the rash? I mean, any risk patient? Any type of group of patients? Any disease? Other drugs that you would be worried about in the sense that, you know, lots and lots of

different types of patients get pneumonia?

DR. LEGGETT: Anybody you would say not to use this drug? Use another one? I think the answer is no. Dr. O'Fallon?

DR. O'FALLON: A comment, I notice in looking at the incidence of events, again from the FDA slides on page 25, the incidence is roughly three times higher in the gem. group than in the comparators, and that is true for any of the events, and the severity seems to be about three times higher at every level--mild, moderate, severe.

What I found intriguing was on the next page where there is rash by indication, it shows that rash in CAP seems to be about three times higher than the rash rates in ABECB. I am curious. Why would that happen?

DR. LEGGETT: That was the age.

DR. O'FALLON: Was that the age deal? Okay, fine. DR. LEGGETT: Dr. Patterson?

DR. PATTERSON: Well, I think it is a good idea to do the five-day and seven-day pack thing because the rash incidence goes up so high after seven days. But a concern is that in atypical

pneumonia, or really any kind of pneumonia but especially atypical pneumonia it is very common to have a persistent cough after the pneumonia has cleared, just from reactive airway disease. I know that very often that gets treated by a repeated course of antibiotics rather than an inhaler. A good example is the Z-pack. I know people who have taken two, three and four just for a persistent cough.

So, I think it should be a very big part of the education and/or marketing that, you know, if someone has a persistent cough you don't give them another refill of the seven-day pack, not because the rash is medically significant--I think we have kind of answered that question, but, for one thing, I think it is significant to the patient to have a pruritic rash for a week. Maybe I am biased because several weeks ago I got my small pox vaccine and it itched like crazy for a week and I couldn't sleep well.

The other thing is that just with the rash, as we have already talked about, even though there may not be cross-sensitization, physicians are afraid just medically-legally these days to give the same class of drug to people who have had

a rash and patients are afraid too. I mean, I have had a patient who said he was allergic to penicillin but he tolerated Augmentin for two weeks in the past and when I suggested using it he thought I was trying to kill him. So, I mean, I think there is a very big perception by the physician as well as the patient that these rashes are significant even though there may not be cross-resistance. So, I think that is another good reason to try to avoid them by not giving more than seven days.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: Just two point. I think that the sponsor did a nice job in showing histopathology. That was really helpful. On the other hand, I think that the way we were taught I don't believe that I have any time rechallenged a patient, and most of my patients don't want to be rechallenged. I feel that when you weigh in the balance this severity, let's say, of acute exacerbation of chronic bronchitis it is probably not worth it and most patients and physicians will feel that way because the patients that developed the rash felt that it altered their life significantly. So, one way perhaps to handle this

would be in the labeling and also intense provider education.

DR. LEGGETT: Dr. Proschan?

DR. PROSCHAN: So, is this largely a psychological problem?

[Laughter]

I ask partly because I get rashes sometimes for no apparent reason and I just ignore them and they always go away.

DR. LEGGETT: That is why the rate in men is lower in these studies!

[Laughter]

DR. PROSCHAN: What are the doctors and patients worried will happen if they just don't do anything? What is the concern?

DR. ADKINSON: It is worth pointing out that the rash for placebo treatment in the 344 study was 3.9 percent. So, just hyper-surveillance for rash will produce a fairly high rate of them. I think in this 344 study we have seen large numbers because people were looking very carefully and observing something that might otherwise in many cases have been ignored and certainly never have come to medical attention.

DR. LEGGETT: Dr. Cross?

DR. CROSS: I practice in a cancer center and I just want to bring up a point which perhaps is slightly off the point but related, and that is that perhaps most abused drugs in a situation of, let's say, neutropenic host are the quinolones. The practice has been that as long as a patient remains neutropenic, if they are on antibiotics, they remain on the antibiotics until they cure their neutropenia. We have lots of patients who resolve their fever; they are stable and are sent home, off-label, on quinolones and stay on that. I have a real fear if it is used in this way, although it is not with the blessings of the sponsor or the FDA. Is it possible to even have something in the insert that this drug is approved for CAP; that it is not to be used for prolonged treatment of neutropenia in immunocompromised patients because these are the ones where I am sure you will see skin reactions triple and all the other complications. I am not sure we have ever had in a package insert that a drug is not to be used for a certain indication, but in view of the prevalence of the problem I think it is worth considering.

DR. LEGGETT: Dr. Drake?

DR. DRAKE: Who asked the question about any group of patients where you would not use it? Was it you? I started to say something very respectful and say lawyers--

[Laughter]

--but I do think that the legal issues become very, very dicey in this arena. On the other hand, I think as professionals it is our responsibility to do what is right for the patient and to be thoughtful about how we make our decisions. That is why I have said what I have said, that we shouldn't just automatically be reactive and say they should never have the drug because they had a rash once because that is not an indicator in my opinion.

But the second thing I wanted to be sure and mention is in terms of Phase IV studies, if it should go that way. I don't think there was a lot mentioned about mucus membranes. You know, Stevens-Johnson and TEN often appear initially, I mean sometimes it is your first clue. Frankly, when you are dealing with diseases of the eye, they can go south pretty quick. You know, two or three days and you can have some visual impairment. So, I would like to have some special--I am sorry there

weren't pictures or biopsies of mucus membranes in this wonderful study that they did, but I would like to strongly recommend that special attention be paid to people who might have a mucus membrane reaction. I can tell you that in that group I would be particularly cautious about rechallenging.

DR. LEGGETT: Before we leave the rash, between the lines I got the impression that none of you were very worried about what has been manifested so far so could I have you speak about definitely showing an increased rash risk that you could identify from the data, recognizing that the numbers are small?

DR. BIGBY: I would say that the rash that has been manifested is not one that I would worry about.

DR. LEGGETT: Dr. Drake?

DR. DRAKE: And I would say that too with one exception, and that is the patient who had the fever. I would pay careful attention to that type of thing.

DR. LEGGETT: Dr. Rodvold?

DR. RODVOLD: Most of these people are going to have fever if they have an infection.

DR. DRAKE: Details, details, details!

Picky, picky, picky!

[Laughter]

DR. PATTERSON: Probably not by day seven or eight.

DR. LEGGETT: John?

DR. BRADLEY: I have a question for Dr. Poretz. I have mostly a hospital-based practice and, as a pediatrician, certainly don't take care of many women under 40. But as someone who is trying to give recommendations for treatment, what I would like to do is to ask someone who is actually in an office, writing these prescriptions every day, how the incidence of rash in the under 40 women would impact his prescribing practices, assuming that the drug does get approved.

DR. PORETZ: I will try to answer that. You know, medicine is never black or white. We always have to make decisions every day. We see people all the time for whom, for various reasons, you want to use certain drugs. For example, sulfa-trimethoprim is a commonly used drug. We like to use it because it is inexpensive. I realize it has a significant amount of drug eruptions associated with it but, you know, many times prescribe it anyway because it is good; it

works under certain circumstances and it is cheap. So, you realize that X percent of people develop a rash.

Well, this particular drug has a higher incidence of rash in certain populations. So, to be crude, I would probably not use it in women on birth control pills commonly and use it in older guys who smoke a lot. Okay? I mean, it seems to have a nice niche for people who have chronic lung disease, people who smoke a lot and people who have community-acquired pneumonia. Maybe that will be patients in nursing homes and maybe it will be people in extended care facilities. I am not sure you are going to use this drug that much in the hospital, in all honesty, because of the reason we said before, people tend to be on parenteral medications.

But in answer to your question, in selective groups of individuals it looks like, because of the MICs--and people can argue that--it will be a very nice drug to add to our armamentarium to treat community-acquired pneumonia particularly.

DR. LEGGETT: Dr. Epps?

DR. EPPS: Just one last brief group for

education would be the pharmacies, particularly when they go to the pharmacy and they get a page-long explanation of what the complications are and what your potential side effects could be and it may not agree with what the prescriber believes.

DR. LEGGETT: Go ahead, Keith.

DR. RODVOLD: Actually, on the slide it really only said educating physicians. I would broaden this way up because the triage is lots of other healthcare people. So, when you look at this educational program, once you get to it, it is going to have to be huge, in my mind, and I mean lots and lots and lots of education and lots and lots and lots of people.

DR. LEGGETT: Jan?

DR. PATTERSON: I was just going to say before we leave the rash issue, regarding postmarketing or Phase IV studies, I had some concerns that Dr. Epps brought up earlier about people of color. At least, in that 344 study there were a fair number of Hispanics, about five percent, but there were only two African-Americans, or 0.2 percent. While there wasn't a difference in the overall studies, I think that would be something to focus on in postmarketing.

DR. LEGGETT: Go ahead.

DR. CONJEEVARAM: From the perspective of not treating these patients on a regular basis, a question I have is that it is true that the current standard of practice for most physicians is that if someone develops a rash you don't rechallenge them. You can talk all you want about that this is safe. We do that in our specialty too with some of the medications we give and we go through the rash, but in general, especially with antibiotics, my impression is that if you do treat someone and they get a rash you don't rechallenge it.

If you take the setting of acute exacerbation of chronic bronchitis, which is a recurrent phenomenon, and as we make guidelines would you use this antibiotic as first line knowing that if there is a high incidence of rash you will never be able to use that again in that setting? That might actually be quite clinically important at a later time.

DR. LEGGETT: That was the reason for my comment about the niche of the resistant bugs. Go ahead.

DR. ADKINSON: If we are treating, for example, acute bronchitis and consider using this

drug, the expected rash rate will be lower than if one chooses to use amoxicillin. So, I think we have jumped to conclusions about the clinical significance of this that are far beyond what is practically the case when you are in a prescribing situation. I mean, I don't see any particular reason to be concerned about the use of this drug for these two indications. If there are high risk groups that can be easily identified, then one would naturally stay away from those groups but for these particular indications the rash rate is not going to be substantially different from the alternatives, it seems to me.

DR. LEGGETT: Dr. Bigby?

DR. BIGBY: Well, in the actual data in the study in head-to-head trials with amoxicillin and Augmentin the rate that is higher, more than twice as high in the head-to-head studies that they presented. I mean, that is clearly not going to be the case.

DR. LEGGETT: If it is okay with everyone else, it is 3:30 and we have two members who have to leave at 5:00, we will skip the afternoon break. If folks have to skip out, that would be fine as long as they come back. Can we move on to the

hepatotoxicity issue? Hari, could you give us your view?

DR. CONJEEVARAM: I think in general, at least from the data presented and from the point of using it for five or seven days, it seems very safe in that it is reversible. None of the findings suggest that they are at risk of going on to acute liver failure, using the Hy's rule.

The only two concerns I have, and maybe Jim Lewis or someone can comment on this, is that if, for whatever reason, you do use a higher dose or you prolong the dosage, if you look at the data from using the 640 mg, it is associated with increased ALT plus increased alkaline phosphatase which is cholestatic hepatitis. So, those patients are not really at risk necessarily of liver failure, which we all worry about but. As we know, there are antibiotics where one of the other potential risks is irreversible bile duct injury where they go on to have prolonged cholestasis, sometimes going on to liver failure.

So, that would be one concern. That is where I think really education about use of this drug for a limited time period might be important and also surveillance post-approval, if it is

approved, to really follow these patients, especially patients who are being treated for longer than what is prescribed. Again, I think probably in a certain number of patients it will be prolonged beyond one week or two weeks and really I think it is very important to follow those patients.

The other issue is patients with underlying liver disease. I am not sure if among those patients there were patients with actual cholestatic liver disease included in the studies. We don't have the details on that. Again, maybe someone can help us with that.

I am really not too worried about the fact that there was a higher rate of further increase in these patients because when we see patients who already have chronic liver disease, we are really looking at their baseline ALT which is usually abnormal, two or three times abnormal as the baseline cut-off. You really cannot compare with a normal ALT in that setting. You really have to say, well, what was the patient's baseline and then how many times beyond that has it increased. The data presented here again shows that though you do have a further rise, they all come back to their

baseline, if not even better actually. So, I don't have much concern from that perspective.

DR. LEGGETT: Are there any populations that you know of, other than sort of idiopathic, that are at increased risk of severe cholestatic hepatitis?

DR. CONJEEVARAM: As far as we know, no. At least there doesn't seem to be any risk when you look at gender, though in general females are a bit more higher prone for drug-induced liver disease. No information on race, not that I know of.

DR. LEGGETT: Dr. Sjogren, could you please put in your two cents?

DR. SJOGREN: Yes. First I want to congratulate the sponsor and the FDA for the analyses of the data. It made it very easy for my review in terms of liver tests. Looking at the group of people with normal ALT and then the group with abnormal ALT, I can make some congruent decisions and opinions.

I agree with my colleague that it doesn't alarm me. It is something that is not unusual for me in the clinic to see these elevations, the percentages that the drug produced, and I was very comforted by the fact that the abnormal ALTs, when

they discontinued the drug, went back to normal in one or two days after discontinuation. So, if people had a normal ALT to begin with I think this situation is not alarming.

For people with abnormal ALT and presumably chronic liver disease, I am also very glad to see that the sponsor took steps to study those kind of patients because that is where we have to use our intuition most of the time because other drugs have not studied patients with chronic liver disease. So, I am very satisfied to see at least an effort in that regard. They had a couple of patients where the elevations were more sizeable and worrisome probably to clinicians at the time, but also when they discontinued the drug the ALTs went back to normal or to baseline, or in some cases improved.

We have no information on the basic kind of diagnosis of those patients but I guess, you know, that may or may not be relevant. The fact that some patients had elevated alk. phos., yes, it points to a cholestatic type of liver condition which in general in our field we call bland cholestasis because it usually doesn't make you think that the patient is going to develop liver

failure, which is what worries us the most.

I would think that if a patient develops jaundice, Hari, the clinicians are going to take that patient off the drug. They just won't continue on it, especially when there are other antibiotics that they could use. So, I am not at all alarmed by what I have seen in the data that was presented today.

DR. LEGGETT: Are there any postmarketing studies or any more data that either of you would like to see?

DR. CONJEEVARAM: I would think only if it is being used for prolonged periods, otherwise I don't think so. The other issue is the issue of isolated hyperbilirubinemia, which doesn't concern me at all actually because usually isolated hyperbilirubinemia doesn't always suggest underlying liver disease. Some of these patients can have Gilbert's when they are under stress where, in fact, the bilirubin does go up. I suspect it is most likely that rather than real liver disease.

DR. LEGGETT: Thank you.

DR. SJOGREN: I would make a plea to continue on--especially the FDA--to continue on

this path for other antibiotics or these kind of drugs to study patients with chronic liver disease because this was very valuable.

DR. LEGGETT: Dr. Epps, go ahead.

DR. EPPS: Do you have any recommendations about alcohol consumption or other drugs, or anything?

DR. SJOGREN: In hepatology we don't want anybody to drink, of course.

[Laughter]

DR. LEGGETT: Does anyone have any comments on the QTc issue as regards gemifloxacin? It was my take that it sort of puts it right smack in the middle of the other fluoroquinolones. Any dissent? Go ahead.

DR. GLODE: I wonder if now is the time to ask about a side effect that wasn't reported?

DR. LEGGETT: Perfect.

DR. GLODE: I am just interested and I have to ask this question as a pediatrician and it goes to the beagle puppies and their arthropathy. I am sorry, it is probably here and I missed it but I want to know if the study design was such that the sponsor attempted to capture all encounters with the medical system for some period of time

after starting the drug. I wonder if that was 30 days or 60 days. I specifically want to know if there was any tendon rupture or tendinitis that was reported that we didn't hear about.

DR. LEGGETT: Dr. Patou?

DR. PATOU: There were no tendon ruptures or tendinitis in the clinical trial program.

DR. GLODE: And what was the ascertainment for that? How long?

DR. PATOU: I am sorry, the studies followed subjects for 30 days post therapy.

DR. GLODE: Great, and you captured all medical encounters?

DR. PATOU: Yes.

DR. GLODE: Thank you.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: Just in the same vein, I didn't notice anything mentioned about neurologic abnormalities so I wanted to know did you notice anything.

DR. PATOU: No is the answer. Although I didn't dwell on it, on the slide that I showed with the overall incidence of adverse events some of the CNS related adverse events were actually lower on gemi. than the pooled comparator. But certainly in

terms of seeing any specific issue neurologically, that has not been the case with the drug.

DR. LEGGETT: Could we spend maybe five or ten minutes at most to think about things on our "want/wish" for further studies that have not been mentioned, or address specifically the blister pack issue, those sorts of things? Dr. Maxwell?

DR. MAXWELL: While I agree that the rash may not be life-threatening, it is certainly morbidity inducing and it is an additional doctor visit, probably several additional doctor visits and unhappy patients. Depending on what the patient does or does not do, it is physically disfiguring to some extent. So, I would like to see more emphasis to look at exactly why women seem to be more at risk, and what is it about estrogen, if it is estrogen, that seems to increase the risk and certainly labeling, if it is approved, should address this really clearly for the clinicians to be able to deal with it.

DR. LEGGETT: Dr. Bigby?

DR. BIGBY: As someone who does not treat CAP, I certainly won't tell the infectious disease people here about efficacy but I am always very interested in numbers with regard to the evidence

that something either is or not efficacious. I think that Dr. Alivisatos has pointed out something very important, that the justification for its being efficacious in the treatment of CAP is based on a single randomized, controlled trial of only 228 patients.

DR. LEGGETT: As you can tell from the looks, we have been down this road before. I don't see anybody jumping on blister packs. Go ahead, jump to wherever you want to go.

DR. BRADLEY: I was going back to the under 40 age cut-off. In talking with Dr. Powers when he had reviewed the previous gemi. submission, the 40 cut-off was apparently something that had to do with acute exacerbation of chronic bronchitis so it seemed a natural cut to look at adverse events as well. If, for some reason, it is actually premenopausal women that have this high rate of reactions, then I think if there is going to be some package labeling which looks at adverse events, as per Dr. Patou's last slide in his presentation, perhaps that sort of information would go in rather than just under 40.

DR. LEGGETT: Anything else? Dr. Goldberger, I was just going to ask if you wanted

us to say anything more.

DR. GOLDBERGER: Well, we still have all the dermatologists here so perhaps I can get them to do some of our work for us. As you know, if this drug is going to be recommended and ultimately approved, we are going to have to write a label so we have had a lot of discussion. But what I would like, if you don't mind, is if each of the dermatologists could give a line or so on these two questions in terms of what should go in the label.

The first is for the person who develops a rash while on therapy, what the label should say about what should be done. Second, for the patient who has developed a rash on therapy, what the label should say about future exposure to this drug and drugs of the class, keeping in mind that at the end of the day we are obliged to do the best we can to make such information available to both practitioners and patients in a way that is clear to them and, hopefully, something that they can actually use. So, I wonder if we could sort of get each of the dermatologists just to briefly address what we should put in the label.

DR. LEGGETT: Who wants to volunteer?

DR. BIGBY: I think that in the

description of the drug for the patient you would have to say that there is a relatively high rate of a mild drug rash that occurs, and you can sort of give a range of percentages based on trial data and also indicate that the rate is much higher in premenopausal women.

I think the management of this type of drug eruption really is just withdrawing the drug and symptomatic therapy. With regard to what should happen to them thereafter, I think that for those patients in whom it is clear that it was a drug rash, I don't think that they should get that specific drug and I don't think we are actually in a position to make a rational statement about the entire class.

DR. EPPS: I agree with those statements. I don't have enough information to say whether or not another drug from the same class could or could not be given. As far as his statements, I think that is appropriate. I might also add what percent were considered severe since they were dermatologist evaluated. That could be helpful.

DR. GOLDBERGER: You would again also say that in a person who developed a rash while on treatment the drug should be stopped?

DR. EPPS: Yes.

DR. GOLDBERGER: Is that what you meant, that this particular drug but not necessarily other drugs of the same class should not be given again?

DR. EPPS: Right. I don't think I have enough information to say don't give one of the others.

DR. ADKINSON: I would disagree. I think it would be a mistake to put anything in the package information about the management of these drugs because we don't have any evidence-based data to make a recommendation, and to put it there makes it become standard of care and really is an impediment I think rather than a help to most physicians. As far as I know, there is no precedent for that. You don't have advice on management of adverse cutaneous reactions to other drugs that are licensed so why bring it up as a particular issue here? The management is going to be the same based on medical considerations regardless what the source of the rash is. I would argue against putting any specific advice if we don't have any evidence to recommend a particular course of action.

DR. GOLDBERGER: Your recommendation then

would be to describe or not to describe what was observed?

DR. ADKINSON: Describe the risk factors so far as they are known, but leave the management of the rash to the physician.

DR. GOLDBERGER: And say nothing about what should be done. Okay.

DR. LEGGETT: Finally, Dr. Drake?

DR. DRAKE: I have to think about it for a moment. May I start with a question first? The reason I was thinking about it is I don't recall any other drugs where you dictate--not dictate but make recommendations on management in this particular arena.

DR. GOLDBERGER: We certainly provide information about certain situations with regards to toxicities in general that may warrant discontinuing a drug. How much have we done? We certainly haven't in the anti-infective world had to deal a whole lot with the issue of what to do about the issue of rash.

The reason in part why I am asking is at the end of the day, in spite of some of the comments we have heard, it seems to me the majority of the evidence here suggests that rashes, at least

in some patient groups who under normal circumstances would be likely to be exposed to this drug are fairly high relative to other drugs. I have heard some people say that there was no comparator in the 344 trial and, therefore, the fact that it is 32 percent--you know, we really can't interpret that. But, of course, there was a comparator, another fluoroquinolone, and the rash rate was six or seven times as high.

So, our concern is if there is likely to be a common adverse event and we are silent, what it does in essence it sort of leave the burden then on the physician and the patient to figure out what to do. Maybe, in fact, at the end of the day, as Dr. Adkinson suggested, that is the best thing to do. Since we are not sure what to say, we just don't say anything and they are left to figure out what they are supposed to do with this, what they are supposed to do in the future, although that is not an easy thing for the average practitioner and patient to have to deal with.

So, I think at the minimum we ought to have this type of discussion and get some feeling from people who at least have either, (a) a lot of experience in the area and/or, (b) at least have

heard a lot of the information presented here in detail, and get some sense of what they think about this. Then, if we decide that it is sounds like people think we shouldn't say a whole lot, then at least it was on the basis of a lot of discussion. But I think it would be a mistake to just assume, well, let's not say anything even though we have a concern that some large groups of people might end up having a rash.

Interestingly enough, one of the reasons to say something might be that many people seem to believe that the rash actually is not of that much consequence, and if you were to make a statement in the label saying that, that might, in fact, be reassuring to some people.

So, those are some of the issues that I think should at least be addressed in terms of deciding how to proceed.

DR. DRAKE: If I can get away with not giving my opinion, I am happy to do so.

DR. LEGGETT: No.

DR. DRAKE: I guess I tend to believe that you should keep it as factual as possible. We have observed this rash in a disproportionate amount in women under age 40, etc. Maybe I am coming from my

own personal bias because I chaired the guidelines of the Care Committee for the American Academy of Dermatology for so many years and what I have learned is that it is very hard to mass dictate what an individual doctor does with the individual patient and I don't think you should put the physician in the position of not being able to prescribe something they think might really help that individual patient without being there at the bedside and understanding what is going on with that patient.

So, I lean towards just giving the provider of care, whether it is your pharmacist, your nurse of your physician, whoever is providing that care, the facts. These are the factual issues as we know them. Then, I think anything beyond that should be--I would vote for putting in a statement that this level of rash perhaps is--you might even want to mention that this has not been seen in other drugs in this category so that will preclude the use of them. But, at the same time, I would hate to have you preclude the use of this drug when it might have a very important role. So, I think I would just leave it factual and let the patient and the care provider make that decision as

individuals.

DR. LEGGETT: Dr. Wald?

DR. WALD: I agree with you entirely. Would it be helpful also to add data about the number of patients in the original clinical trials who did continue to receive treatment despite the fact that they developed a rash? I don't know if you have a number that you could attach to those who continued to receive treatment who did okay, in what proportion of patients that was. And then give the cipro. data because although it may not represent what would occur with any other fluoroquinolone, at least it would be a piece of data that suggests that at least for one the cross-reaction rate was quite low.

DR. LEGGETT: Dr. Reller?

DR. RELLER: Actually, Dr. Wald has probably already brought up perhaps the most important point, other than the relative increased frequency, and that is the data for lack of cross-reaction because the very group of patients who have the highest likelihood of a rash are the group of patients who are most apt to see a quinolone, for example for a urinary tract infection.

DR. LEGGETT: Go ahead, Mark.

DR. GOLDBERGER: I think that was very helpful. That provided us I think with at least enough information to get some idea how we might want to proceed.

DR. LEGGETT: Ken?

DR. BROWN: Mark, I was going to comment that the precedence for such a teaching statement goes back to nitrogen mustard where it says be careful and wear gloves if you are giving this drug and then the boiler plate for all beta-lactams which says what to do in case of anaphylaxis. But I think trying to turn the package circular into a teaching instrument or a Merck Manual would be a terrible mistake.

DR. LEGGETT: But it doesn't have to go as far as the sort of QTc worry.

DR. BROWN: Well, I have drafted some wording but I don't think it is important for me to share that right now.

DR. LEGGETT: You can give that to him later. That would be great. Since it is now four o'clock, why don't we pass on to addressing these three questions? Everyone here at the table, except Dr. Brown, is a voting member. As we go

around, what I would like to do is hear your vote and then a brief summary of your reasons for a yea or a nay, understanding that there are many of us and there is only an hour left. Judging by the way the day has gone, I just thought I would make that clear.

Though I do not think we necessarily need a vote for the FDA's purposes on questions two and three, I would like to address both two and three at least in brief terms so they get a better idea of what to do, no matter which way they take our 50-50 vote. John, do you want to write a little longer or do you want to be the one to start?

DR. BRADLEY: I would vote for acceptance of community-acquired pneumonia, except for the severe category where I think that the data are insufficient at this time to give that approval.

DR. LEGGETT: That is a yes for community-acquired pneumonia for mild to moderate?

DR. BRADLEY: Exactly. Yes for acute exacerbation of chronic bronchitis. In terms of adverse events, to have the package labeling somehow document the increased risk of rash so that it is something that is understandable by clinicians for the appropriate age group and sex.

Then, in terms of the specifics for the subsets of pneumococci that are resistant to other antimicrobials, my preference would be to turn the clock back and just go by in vitro susceptibilities but if what Dr. Powers says is true and the cow is out of the barn, then I think simplifying the approval for multi-drug resistant Strep. pneumo. based on criteria that I think we will be working on would be appropriate because it clearly recognizes the fact that gemi. is active against penicillin-resistant, macrolide-resistant, cefuroxime-resistant strains.

DR. LEGGETT: So, that is a yes for NDRSP?

DR. BRADLEY: Yes.

DR. LEGGETT: Dr. Maxwell?

DR. MAXWELL: I vote yes for community-acquired pneumonia, mild to moderate disease certainly, and I echo what John has said about the multi-drug resistant bugs.

On acute bacterial exacerbation of chronic bronchitis I vote no. I think that while the issue of the other two adverse events, the hepatic toxicity profile and the cardiac toxicity, is really not of great concern. For me the rash still is a concern and I believe that it should be

evaluated more in depth.

Having said that, I also believe that even though the rash may not be life-threatening in the few patients that we have seen, I think it will impact on the practicing physician. I know that I would be hesitant to do so because most of my patients, once they develop a rash, and this is a generalized rash, develop great concerns. So, I would like to see more studies on why women seem--

DR. LEGGETT: We will get to that later. Dr. Poretz?

DR. PORETZ: For community-acquired pneumonia I vote yes and for exacerbation of chronic bronchitis I vote yes, and I will explain why for both of those.

I think the data that we are recognizing more and more with the fluoroquinolones and seeing the resistance to Strep. pneumoniae is a real thing. I think the people from Canada showed that in the past. It is happening in the United States; it is happening in other parts of the world, and I think there is probably no reason to believe that it is not going to continue. If we don't approve this drug we could wake up in a year or two and have a significant amount of resistance to

fluoroquinolones to Strep. pneumoniae. For that reason, I think it is very important to get this drug on the market and use it for those indications.

I like the concept of multi-drug resistance to Strep. pneumo. I like that as an indication. I think that sums it up very, very nicely.

DR. LEGGETT: Could you address in community-acquired pneumonia where you would include severe?

DR. PORETZ: I think it is going to declare itself, in all honesty, because those people, as I said before, who are severely ill are going to be in the hospital and are going to get parenteral medication. I am not against leaving off the word "severe" but I think it is going to declare itself so I don't feel very strongly about it. That is going to be a clinical decision.

DR. LEGGETT: Dr. Goldberger, if we forget to make sure that you have enough information about the why's or the why not's, jump in, please. Dr. Patterson?

DR. PATTERSON: Based on the fact that there is activity against fluoroquinolone-resistant

pneumococci, although it may be small if you consider the area under the curve, I would vote yes for the mild and moderate community-acquired pneumonia indication and for the acute bacterial exacerbation of chronic bronchitis indication.

I would favor the term multi-drug resistant as defined by three classes of clinically used drugs rather than pen-resistant or macrolide resistant.

The other caveat is that I would specify that it is not for prolonged use, particularly not for repeat therapy that would constitute more than seven days, and to specify that there is a high risk of rash in women under 40 years of age and high risk of elevated ALTs in patients with preexistent liver disease.

DR. LEGGETT: Dr. Reller?

DR. RELLER: Yes for CAP owing to mild to moderate Streptococcus pneumoniae. Though it may work for other things, I think the data are insufficient to have a broad claim for all of the other etiologies.

The data are sufficiently sparse in my view for acute exacerbation of chronic bronchitis, especially with the broad number of pathogens

listed. In any individual group there are insufficient numbers so I vote no for that. Not that I don't think that it may work given the largely empirical therapy, and I recognize what has been brought up earlier about perhaps the unfairness of going back but I think the data are sufficiently sparse that I would like to see additional studies on this issue, and including a placebo-controlled trial, not in holding someone to a standard that is imposed after the fact but based on the relative smallness of the studies done to date that don't give me confidence especially for the broad range of indications.

In contrast to others, I want to take the opportunity to voice a no for specific resistance mechanisms. Clearly, in the past and perhaps the present and future there may be promotional benefit to a sponsor to have a specific resistance indication. There may be political plus to the agency for doing something about resistant organisms. But I think some of the things we have done in the past are an ill-advised precedent and, despite the past well-intentioned actions on this issue, I think it creates a deepening dilemma for us. The reason I say that is because what is true

today can't be assumed for tomorrow.

In support of what Dr. Bradley mentioned earlier, I fail to see why we can't have indications for susceptible organisms and, to the extent that a given compound is active, regardless of whether or not a particular organism is resistant to penicillin, macrolide, cephalosporin or whatever the case may be, it enables one to treat. Indeed, the promotion of a compound could be based on the data in vitro, PK/PD, etc. that a compound is active without regard to mechanisms of resistance and then one has a basis for continued use of a drug based on susceptibility even though the ground may shift in terms of resistance, and even within class.

I think there is pretty interesting information presented to us, both on PK/PD as well as investigator susceptibility, and this drug may well be an agent one would go to for quinolone failure for empirical therapy. We don't have the data to specifically make that claim but as long as one had an isolate that was persistently susceptible, or even in a given institution in biograms where the prevalent organisms were susceptible, one could still use the drug

empirically, getting around the argument that in reality you don't usually have an organism in these cases.

So, I think that actually it is an issue that the agency should revisit, and we should emphasize the persistent robustness of some agents versus other agents in the face of increasing resistance and not get into the specific claims that are not apt to hold up for tomorrow necessarily.

DR. LEGGETT: Dr. O'Fallon?

DR. O'FALLON: I want to preface my remarks by saying that I was really impressed by what the company did. I think that this was a good piece of work.

My problem is that when I looked through the information and saw what was going on, I think you have proved or I think the data support the decision that this is not inferior to the things that are out there now. That doesn't mean that any of them is effective. That is what isn't there. But, frankly, that is about as good as it is going to get as far as I am concerned; they are not worse.

But I do think, given the fact that there

is substantial toxicity associated not only with this but with any other of the rest of them--they all have their adverse event profiles, if they aren't doing any better than, say, multi-vitamin capsules three times a day, then we are exposing patients to a lot of toxicity for no real benefit and I think that needs to be sorted out by the business here, the FDA and company. I don't think it is right to change the rules on the company because they did what they were told.

I am not happy with the results but I think that there is the problem of treating people with these agents and then we are feeding the resistance. Every time we treat these patients with something they really don't need or even if it is something they do need, we are feeding the problem of multi-drug resistance or beefing up the resistant organisms.

DR. LEGGETT: Judith, yes or no?

[Laughter]

DR. O'FALLON: No, no, you said and I am going to do it.

DR. LEGGETT: I said briefly.

DR. O'FALLON: Well, see, my problem is I can vote yes to saying it is not inferior. I can't

vote to whether it is any good, and I think that is the problem.

[Laughter]

And, I think there is just not enough information about whether it works in severe disease. There is not enough information about whether it works in resistant organisms. So, a placebo trial is needed but that is not your problem; that is the FDA's problem.

I suggest though when you go to publish your results, I think it is going to be very important to use confidence intervals. These points estimates are ridiculous. We cannot tell what the real range of values is likely to be. I think it is very important to publish the confidence intervals when you go to tell the rest of the world what happened in this study.

DR. LEGGETT: So, we will take that as a yes for non-inferiority.

DR. O'FALLON: Non-inferiority is a yes. That is as far as we go. No on everything else.

DR. LEGGETT: Keith?

DR. RODVOLD: In community-acquired pneumonia I agree. In the mild to moderate indication I would be willing to vote yes. I agree

that the data for severe wasn't there and historically we actually kind of voted for resistant pathogens when you had a very clear picture where there were in vitro models, in vivo models, patients, ICU, bacteremic, everything convinced and lit up so that you were really convinced that bacteremia with resistance, you were going to cover it. So, I am a little hesitant on giving resistance because we don't have a severe indication here.

With that, I would also like to make a comment about the aspect of the cefuroxime-resistant pathogens. I don't even see that that language is needed because that is not a drug you put up in CAP that much at this point and penicillin is predicting a resistance anyway. So, I think that doesn't need to be there, or second generation cephalosporins. I think the penicillin data tells you that.

The multi-resistant labeling, if you do go to it, my comment would be I would not list five or six drugs. I think that is going to be way too confusing to people. I would probably try to stay with penicillin and macrolides only but, again, I am not voting for that.

The second indication of acute bacterial bronchitis, actually I am going to vote yes for it but if I was going to hold back on that indication and wanted more postmarketing safety data, this would be the one I would tell you to hold and get more postmarketing safety data if you thought you needed to do that, and then release it later on as we got convinced. You have done that before with other drugs that you have approved. You have held an indication waiting for more data to come. But I would approve it based on the basis that you followed the trials that you were told to do and you did it. The data could be more though. I think you need more data there and I think it needs to be done better but I think you did what you needed to do.

DR. LEGGETT: I vote yes for mild to moderate; yes for exacerbations of chronic bronchitis. I see no reason from the MIC and other data to believe that this fluoroquinolone, which is a lot like other fluoroquinolones, should not work for H. flu. in CAP but I have a lot of worries about community-acquired pneumonia due to E. coli and Klebsiella pneumoniae and I would definitely not allow the name Staphylococcus aureus to go on

the label for community-acquired pneumonia with this drug. I might have a little worry about even putting aspiration in there because I am a little worried about the anaerobic coverage. The reasons for all of the things are basically what everybody has stated so far.

Regarding the fluoroquinolone multi-drug resistance, I like the concept at least how we have talked about it in the last couple of meetings. While scientifically I definitely agree with Dr. Reller, I think the cat is out of the bag, as he sort of mentioned, and I think that while we can sort of try to stay pure scientifically, this is a world of political and capitalistic compromise so I think that, given that, eventually I would be convinced that this is a multi-drug resistant drug because it is exactly in that small population of folks that I might use this drug, that have seen a lot of fluoroquinolones, that I am worried at least from what we have seen so far. I do not, however, think the numbers for all the different subgroups are big enough yet. So, I would put a yes vote contingent on how many sick, bacteremic, drug resistant folks in the 287 come in. I would also make a caveat not for long use.

DR. WALD: I would vote yes for acute community-acquired pneumonia and yes for the acute exacerbations of chronic bronchitis.

I would agree with some of the others in terms of multi-drug resistance. I think we can feel confident recommending the drug for the empiric management of community-acquired pneumonias. Most or at least many of those are viral. There is a relatively small proportion that are bacterial. Of the bacterial, there is a very small proportion that are really multiply drug resistant and we never know which those are when we begin therapy. So, I think what we are saying is that this is a drug that can be used comfortably for community acquired infections of the lower respiratory tree that can be managed as outpatients. That is sort of where I would draw the line.

I don't know if this committee can exert any pressure on any AHRQ, NIH or CDC to fund the study that we are talking about, which is a placebo-controlled study, because it would be very brave for any of the drug companies to undertake that and I think really, in the end, if it turns out that most of the drugs we use are no better

than placebo that would really be a tremendous advantage to the insurers and to the government. So, I think it really should be a government-sponsored study.

DR. LEGGETT: Dr. Cross?

DR. CROSS: I would vote yes for community-acquired pneumonia. I agree that there hasn't been a lot of data on severe pneumonia. There hasn't been anything on Staph. aureus and I would also agree with Jim that we have no basis for actually including that.

I think it does fit a real niche in terms of the increase in quinolone resistance. I think each of our locales ought to have some information on the degree of resistance. So, I think the idea of having an approval for multi-drug resistance is instructive if you know what is going on in your community. It gives a certain reassurance.

In terms of the exacerbation of chronic bronchitis, I have mixed feelings about this. Seeing the long list of drugs that are already approved, this certainly doesn't appear to be any better or any worse, although I do have some doubts as to whether or not it is efficacious. But the thing I am concerned about is if any patients, by

getting this for this indication, do have a rash and in practice once a patient does have a rash--most physicians haven't had the benefit of the excellent dermatologic consultation we have had here and the reassurance and I think what will happen is that a patient will not get quinolones in the future. That is my main concern. Having said that, I don't think we can hold them to a higher standard although I wouldn't use it myself.

DR. LEGGETT: Dr. Proschan?

DR. PROSCHAN: I am teetering on the edge with respect to community-acquired pneumonia because I still believe that, you know, on page 69 of the blue book, it is no means a slam dunk. That confidence interval, by the way, for study 12 if you look at the intention-to-treat analysis, is actually minus 12.-something, not minus 10.-something. I tend to believe the intention-to-treat analysis more than per protocol anyway. So, it looks to me like the supportive evidence shows that it is better than at least one currently used drug. So, I guess that would tip me ever so slightly for voting yes.

For chronic bronchitis, I agree with the FDA that multiplicity issues were definitely an

issue here. I think when you are writing the results you have to be careful about some of those multiplicity issues. In particular, when I look, for example, at page 64 of the red book and you see the results at all these different visits, I think it can be explained by chance. But overall I felt like the evidence was pretty conclusive that it is at least as good so I would vote yes on that as well.

DR. LEGGETT: Mike, could you give us a yea/no on severe community-acquired pneumonia? You can also abstain.

DR. PROSCHAN: Yes, I think I probably should abstain because I don't know that much about the severity.

DR. LEGGETT: Dr. Glode?

DR. GLODE: I would vote yes for mild and moderate community-acquired pneumonia, again understanding this was designed as a non-inferiority trial. I think the data support non-inferiority but I accept your comments certainly.

I would just have the caveat that I agree with 19 strains of Staph. aureus, and who knows whether that was even the causative organism. That

data is inadequate for staph. or M. catarrhalis, possibly even for Legionella with 14. So, the numbers are small when you do the subsets.

I would also vote yes in terms of non-inferiority for acute bacterial exacerbation of chronic bronchitis. But I am persuaded by Dr. Reller's comments and his reluctance to allow a specific claim for multiply resistant Strep. pneumo.

DR. LEGGETT: Dr. Drake

DR. DRAKE: Well, I feel completely inadequate. I learned a long time ago you don't get in the way of the ID guys or the pediatricians when you are a dermatologist.

[Laughter]

But I must tell you I learned a ton here today and I did read all the stuff you sent me, which is unusual. I read it better than I read the derm. stuff because I actually felt I had to read it because I didn't know what I was doing.

I am going to vote yes on the community-acquired pneumonia but I would like to support what Mary said and what you said and what others around the table said. I think it is mild and moderate. I am not convinced it is adequate

for severe. It may be; I just don't think we know.

I am going to vote yes on the chronic bronchitis, and that is based mainly upon what I have heard here at the table, and I hesitate to cast that vote. It might be better to abstain because I don't think I have the depth of knowledge to comment on that.

DR. LEGGETT: Dr. Bigby?

DR. BIGBY: I guess my comments would be that I think that the drug will have a relatively high rate of producing drug rashes. I think these are predominantly of a minor type and that shouldn't preclude it from being marketed. I think it should contain some warning especially about high rates in premenopausal women, and I don't think I am going to vote because I don't treat patients with community-acquired pneumonia or with chronic bronchitis.

DR. LEGGETT: Thank you. Dr. Epps?

DR. EPPS: From what has been heard and what I have read, I guess I would be in support of mild to moderate community-acquired pneumonia, as well as the bronchitis indication. Certainly, I think clinicians need options. I would support many of the comments regarding facts regarding the

344 study, the brevity of the course as well.

DR. LEGGETT: Dr. Adkinson?

DR. ADKINSON: I would vote yes on both indications, largely deferring to what I think is a consensus of my infectious disease colleagues and I certainly accede to their views on the issue of multiple resistance, about which I know very little.

My yes vote certainly includes my own assessment that I don't think this rash problem is sufficient to deny approval for a drug that otherwise has a clinical niche. I think that is especially true for the bronchitis indication where the expected rash rate will be very low.

DR. LEGGETT: Thank you. Dr. Hilton?

DR. HILTON: I feel that the high potency of the gemi. drug works strongly in its favor for me, and I feel that if I were the patient being treated getting over my community-acquired pneumonia would be much more important to me than experiencing a bout of rash. So, I vote in favor of the CAP but with the restriction on stage V of the Fine criteria.

On the chronic bronchitis, I feel that the youngest patient studied was 34 years of age and I

feel that there is essentially no data in young people and it should not be considered for approval for young people. The average age was 60 and higher for the patients in those studies.

I also feel that even though the standards may have shifted and the drug company wasn't previously requested to do placebo-controlled trials, given what we know now, they are very important. So, I vote no on the chronic bronchitis.

DR. LEGGETT: Thank you. Dr. Conjeevaram?

DR. CONJEEVARAM: I would vote yes for community-acquired pneumonia, mild to moderate. I would vote yes for the acute exacerbation, but I would favor giving it as a second line, especially if they fail other regimens.

Again, my concern is that this is a recurring disease and, to me, the risk of rash is still concerning. I would favor multi-drug resistance labeling. I would also, as some of my colleagues have already mentioned, really discuss on the label about the predictors of rash, who is at actual increased risk. I think that is very important for the physicians who are treating with this drug to know. I would also strongly emphasize

the long-term use, that this is really for five to seven days.

DR. LEGGETT: Dr. Sjogren?

DR. SJOGREN: Yes, I am guided here by the comments from my colleagues, infectious disease colleagues although, you know, I have heard both sides, some pro and some against, and also based on my own opinions as a clinician at a hospital.

I think I would like to vote yes for the community-acquired pneumonia and for the acute bacterial exacerbations of chronic bronchitis, mild to moderate. I think for the severe cases there is little data.

About the drug resistance, I do feel that there is so much drug resistance nowadays that the drug has shown, at least in microbiology, to be quite good about it. I don't know why we have so much resistance to approve that label. For I think for the Staph. aureus I am concerned that there was not enough data but for the rest of the organisms I thought it was adequate so I would vote yes for that as well.

DR. LEGGETT: If I could make one sort of last point for the FDA, there was mention made, regarding this multi-drug resistance status, of

substituting one drug to boost something else. But what we don't know from the data that was presented is how many of these bugs were actually the same bugs so we are seeing the same 12 all over again. If it is really 12 plus 10 plus 6 and we are coming up towards 50, that is one thing. But if it is the same 15, just in different ways, then I think our numbers are not as big as we would like.

Instead of going to question two, since it is now 4:35, can we jump to question three? Let's just assume that our answer to 1(a) and 1(b) is no, what kind of things would people around the table think necessary to be done? One of the things that I would sort of throw out is that I, for sure, think that we need to finish 287 and increase the number of pneumococcal isolates and resistant data. I will shut up and let somebody else throw in their two cents. Barth, you were another hold-out.

DR. RELLER: Well, I think additional data for 3(b) is a placebo-controlled trial, funded by whoever's arm can be twisted to do it for its potential benefits to the taxpayers, third party payers, consortia thereof, brave pharmaceutical philanthropist, anybody who is willing to do it, Bill Gates.

DR. LEGGETT: There was mention made already of postmarketing studies and a study looking at photographing mucus membranes. We already talked about better data for AECB. Someone did mention, in terms of resistance gemi., rash, gemi. again, if more things can be done in that sort of subset. Then I think, of course, if the answer is no or approvable but, I think we would all like to see more cases of severe bacteremic community-acquired pneumonia in terms of that. John?

DR. BRADLEY: In some of the earlier derm. presentations the risks of rash with the drug and the risk of Stevens-Johnson/TEN were listed, and the Stevens-Johnson is always less frequent than the regular exanthem. I am wondering if there could be any systematic way postmarketing, if we could track the incidence of Stevens-Johnson syndrome to see if it throws into the category of sulfa or phenytoin or whether it is something very, very small. I don't know if that is possible but that would be very helpful and would fold into this rash AE story.

DR. LEGGETT: Dr. Reller?

DR. RELLER: Another thought occurred to

me. The 344 study has been lauded by many. I wonder if it would be possible, since our dermatology consultants were of divided opinion on the importance of this rash, as well as the probability of it happening again and, if I recall correctly, some diversity of viewpoint about whether a reaction was for life or for a period of months, is there any possibility of going back to the participants in the 344 study who had a rash to gemifloxacin and giving them a five-day exposure to gemifloxacin? Because if it is 100 percent, that is one thing. If it is five percent, like it was with ciprofloxacin, or ten percent that would be very useful information. Given the general consensus that no matter whether you should or shouldn't ever give the drug again and all of the other things for which I think there was consensus that it was not a serious reaction, certainly not a life-threatening one, nor was the exanthem, Dr. Bigby emphasized, necessarily a prelude to some more serious consequence.

DR. LEGGETT: Dr. Cross?

DR. CROSS: Barth, I like that idea. I think it is worth doing. I would just like to reemphasize the point made by Dr. Maxwell in terms

of looking at the incidence of rash in minorities, especially African-American. I think there were only two subjects in the large study.

DR. LEGGETT: Sorry, I forgot to include that. Yes?

DR. ADKINSON: I was going to say I found it very intriguing and would endorse the proposal of the sponsor to try to manage the rash problem by packaging the drug in five unit doses so that extended courses of therapy cannot easily be given.

DR. LEGGETT: Dr. Rodvold?

DR. RODVOLD: I agree with the aspect of packaging but the problem I have with that is no one was proven to us that it works. I constantly hear about Z-packs being re-prescribed and ABC packs being redone, but I think I would also like to see data that proves this works because it is constantly coming up--we are going to package it this way and this is going to be the save-all of this problem. So, I think that is something that really needs some science put behind it. I don't have a solution how to do it but I think it does tell us something with or not that is a really legitimate reason to put on the table.

DR. LEGGETT: In that sense, could we have

question number two flashed up? Keith, you already talked about information for everybody, especially the front office and the folks answering the phone, and you talked about the Z-pack. In my notes I didn't really notice anything except how long the treatment should be and what to do about repeated courses and how to handle the rash, that sort of thing, in terms of the packaging. Do you want to address that again?

DR. RODVOLD: One of the other things that comes up that I would think could happen is that if, say, you developed a rash but you still wanted to use a quinolone, if you switched to another quinolone do you go into a problem? It goes away? I think there are going to be scenarios where people get into that. They are going to be up against the wall and they are going to switch out of this quinolone and go to the next one, and that would be very valuable information, to know whether or not you can or cannot do that. It is not going to happen a lot but it is going to happen.

DR. LEGGETT: Working in a managed healthcare plan, I can tell you that we don't get the chance to choose any fluoroquinolone we want. So, that is going to come up again too. Go ahead,

Hari.

DR. CONJEEVARAM: I suspect that if this drug is used, especially for community-acquired pneumonia, and if it works for that particular patient and even if they do develop rash it might be used again for that patient. So, I think I would favor for the drug company to really keep track of that data. You are getting your rechallenge data, especially with the rash, in that setting. It will be very important. At the end of the day you can actually show that the drug is beneficial but the risk of rash is not that high or the same.

DR. LEGGETT: Thank you. Any other comments before I ask Dr. Brown to read his statement? Go ahead, Ellen.

DR. WALD: I would like to ask the dermatologists. A rule of thumb that I have used for alleged penicillin allergies when I am treating someone with amoxicillin or ampicillin is that if the rash doesn't itch and it is non-urticarial I use that as an indication to keep going, or if I get that history I feel comfortable repeating or using it again. Is that sound or crazy?

DR. LEGGETT: Or does it just sound crazy?

DR. BIGBY: Do you want a vote? I mean, I would say that there are lots of drug eruptions that don't itch and aren't urticarial and, under those circumstances, if you continue to give it the patient may or may not get worse, and if you let them clear and gave it again the rash would come back, not necessarily that it is a terrible thing. I mean, there are lots of drug rashes that are due to a drug that don't itch and are not urticarial.

DR. LEGGETT: Mark?

DR. GOLDBERGER: Just to ask again, similar to what I did before, about another issue, what kinds of statements--some people have touched upon this already--would you like to see in the label, ranging from very little to a lot, about duration of therapy and avoidance of re-prescribing, and even any comment about multiple courses over time? Some people have touched upon a few of these issues but it is another thing that is important in deciding what kind of information we ought to put in labeling. In other words, the duration and there has been a proposal for a five- or seven-day pack. Linked to that is how strong a statement about really discouraging re-prescribing and, finally, does there need to be any comment

about multiple courses over time?

DR. LEGGETT: I would think in the absence of data it would be better to keep our mouth shut. Is it possible to start off a label that sort of mentions the risk while these other studies might be pursued, and then go back and modify the label specifically at that point? I don't know if that is even plausible but that might be one approach to sort of not say too much until we at least have some data and then readdress it, just as the QTc wasn't put on the packages until we had some data, or the drug interactions with the macrolides and those sorts of things.

DR. RODVOLD: I think when we did some of the other agents, linezolid and moxifloxacin, when we did that we really told people not to exceed the dose and do not exceed the duration. That was pretty much where we stopped at that point. But here you may want to say that longer durations of therapy were associated with a little bit higher risk in selected types of patients. You put it in the inserts because I was the one that made these comments during those times and Jim jumped in with me at least on one situation. We made them at that time because we only knew this amount of

information at this point. If you can put it in multiple places in the insert so, hopefully, it gets read at least once, that is the best you can do.

I would agree with Jim too that eventually you may end up modifying that. That may be a goal that the sponsor and the agency may want to work to be able to change this with time.

DR. LEGGETT: I would also remind the sponsor that what they heard today about physicians being very reluctant to re-prescribe a medication to which there was a rash might be, in itself, enough of an incentive to try to sort out this question if they wanted the drug sold the second time around.

The final point in terms of packaging things, linezolid was approved for 14 days but we now have people using it for months at a time and developing peripheral neuropathy. So, anything is possible. Dr. O'Fallon?

DR. O'FALLON: With respect to the duration of treatment, there is a lot of evidence here. You provided us with a good bit of information about how the rash rate went up anywhere from five days to 15 days of treatment. I

think you can simply explain that the rate, you know, tripled over that period of time. It is a statement of fact based on a very good study and I think you should put it into the label.

DR. RODVOLD: In designing and implementing a clinical trial we typically take many safeguards to minimize the bias and estimate treatment effect.

DR. O'FALLON: But the warning should be to let the physicians know that this rate is going to go up rather substantially over time.

DR. LEGGETT: Yes, Dr. Glode?

DR. GLODE: I would just think as opposed to trying to capture in a Phase IV postmarketing study retreatment episodes and hope you got them, I would think if the dermatologic opinion is split or somewhat divided that maybe it would be worthwhile, in a sort of sequential phase, to take the patients from the study and take ten women who had rash, who had mild to moderate rash, and rechallenge those ten. If ten out of ten get a rash, at least you know. If it zero out of ten, you could proceed sequentially. You don't have to offer it to hundreds of people initially.

DR. LEGGETT: Good thought. Unless you

can think of anything else for us, Mark, I think we are done. Thank you, everyone, for coming and for sitting through a long day. For the committee, I believe tomorrow we start at 9:00 a.m.

[Whereupon, at 4:50 p.m., the proceedings were recessed to be resumed on Wednesday, March 5, 2003, at 9:00 a.m.]

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CERTIFICATE

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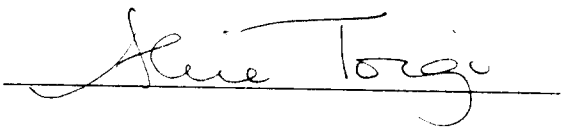

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