DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

Gaithersburg, Maryland
Tuesday, September 12, 2006

P R O C E E D I N G S

8:00 a.m.

DR. EDWARDS: Good morning, and welcome to the September 12, 2006 Anti-Infective Advisory Committee Meeting. In order to -- we re going to try to stay on time as much as possible during the entire meeting today in order to be fair to everyone involved to have equal time for presentation, and so without further ado, I m going to start with the introductions.

My name is Jack Edwards. I m the head of the Infectious Disease Section at the Harbor-UCLA Medical Center. We re going to begin with the introductions, and then we ll move on to the conflict of interest statement.

Let me begin at the far end of the table with Ed.

DR. COX: Yes. Good morning, Ed Cox, the Acting Director for the Office of Antimicrobial Products.

DR. ALBRECHT: Hello. I m Renata Albrecht, Director of the Division of Special Pathogen and

Transplant Products.

DR. POWERS: John Powers, Lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives in the Office of Medical Policy.

DR. SACKS: Leonard Sacks, Medical Team Leader for the Division of Special Pathogens and Transplant Products.

DR. TIERNEY: Maureen Tierney, Medical Reviewer, Division of Special Pathogens and Transplant Products.

DR. MOSHOLDER: Andrew Mosholder, Medical Officer, Division of Drug Risk Evaluation, FDA.

DR. GARDNER: Jacqueline Gardner, University of Washington, Department of Pharmacy.

DR. GUTIERREZ: Kathleen Gutierrez. I m on the faculty of Stanford University School of Medicine, and I do pediatric infectious disease.

DR. FROTHINGHAM: Rich Frothingham, Department of Medicine, Duke University.

DR. BRADLEY: John Bradley, pediatric infectious diseases, Children s Hospital, San

Diego.

DR. MOSADDEGH: Sohail Mosaddegh. I m the Designated Federal Officer for this advisory committee.

DR. KAUFFMAN: Carol Kauffman. I do infectious diseases at the University of Michigan in the VA Hospital in Ann Arbor.

DR. TUNKEL: I m Allan Tunkel. I m Chair of the Department of Medicine at Monmouth Medical Center and do adult infectious diseases.

DR. TOWNSEND: Greg Townsend, University of Virginia, infectious disease in the Department of Medicine.

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

DR. PORETZ: Donald Poretz, infectious disease in Fairfax, Virginia.

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

DR. WONG-BERINGER: Annie Wong-Beringer,

University of Southern California, School of Pharmacy.

DR. GROSS: Peter Gross, Infectious Disease Specialist, Chair of Medicine, Hackensack University and Medical Center in New Jersey and a former Chair of FDA s Drug Safety and Risk Management Advisory Committee.

DR. WIEDERMANN: Bud Wiedermann, pediatric infectious diseases, Children s National Medical Center and George Washington University.

DR. MALDONADO: Sam Maldonado, District representative.

DR. EDWARDS: Thank you. I will turn the conversation over now to Sohail Mosaddegh, who will read the conflict of interest statement.

DR. MOSADDEGH: Good morning. The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda, 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 with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), a full waiver has been granted to Dr. John Bradley for unrelated consulting for a competitor, which his employer receives less than $10,001.00 per year.

Dr. Peter Gross has been granted full waivers under 18 U.S.C. 208(b)(3) and 21 U.S.C. 355(n)(4) for unrelated consulting for unrelated consulting for a competitor, which he receives less than $10,001.00 per year, and for stock in a competitor valued from $5,001.00 to $25,000.00.

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.

With respect to FDA s invited industry representative, we would like to disclose that Dr. Samuel Maldonado is participating in this meeting

as an acting industry representative, acting on behalf of regulated industry. Dr. Samuel Maldonado is employed by 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.

DR. EDWARDS: Thank you. I d like now to introduce Dr. Renata Albrecht, who is the Director of the Division of Special Pathogens and Transplant Products. Dr. Albrecht will make some opening remarks, review the quinolone drug development, with emphasis on post-marketing safety.

DR. ALBRECHT: Thank you, Dr. Edwards. I realized I was saying good morning to everyone this

morning and forgot to double-check that I had all those electronic gadgets I need to advance the slides, so I ll appreciate any help on that.

First of all, I wanted to say good morning and welcome everyone to today s advisory committee on the subject of Factive, also know as gemifloxacin, for the proposed indication of acute bacterial sinusitis. I d like to also say thank you to Oscient, the sponsor of this application, as well as all our colleagues at the FDA for all the work that they have put into preparing, reviewing, this application, as well as in preparing for today s advisory committee.

And very importantly, I d like to thank Dr. Edwards for chairing today s committee, as well as the other distinguished members and consultants to the committee that have joined us today in Gaithersburg to help us with the discussion of this very important and challenging application.

Before I actually start my introductory remarks, what I wanted to do actually is mention that two of the committee members will actually be

rotating off, and we d like to thank them very much, Dr. Poretz and Dr. Bradley. We do have certificates that will be given to you, but they haven t quite been brought in today, so they will be mailed to you. Again, on behalf of myself, as well as Dr. Sureth of the Division of Anti-Infective Drug Products and Dr. Cox, our Acting Office Director, I wanted to express our great appreciation for your service to the committee. I also wanted to welcome our two newest members, Dr. Annie Wong-Beringer and Dr. Bud Wiedermann, who are joining us for the first time today, so welcome.

Next slide, Sohail. What I d like to do this morning is give you a brief overview of the application and the issues before us, and cover, basically, the proposed indication, talk a little bit about the approved indications, the review that s facing us with this application, mention a little bit about adequate and well-controlled studies, and finally, give you the questions that we would like you to debate and vote on this

afternoon. Next slide.

So Oscient has submitted an application for the proposed indication of acute bacterial sinusitis due to streptococcus pneumonia, haemophilus influenza, Moraxella catarrhalis, staph aureus, the methicillin-susceptible strains only, Klebsiella pneumoniae, and E. coli. The proposed dosage regimen is 320 milligrams once a day orally for a total of five days.

As you know, Factive is already an approved floroquinolone. It s approved for the indications of acute bacterial exacerbation of chronic bronchitis due to the listed organisms, as well as community-acquired pneumonia of mild and moderate duration for a number of organisms, including streptococcus pneumoniae, including multi-drug resistant strains, as well.

In the application under discussion today, Oscient has submitted results of five clinical studies on acute bacterial sinusitis, along with safety data from other clinical studies, as well as post-marketing safety data.

Now, what s unique in this application is that the first four studies -- and you ll hear more about the design and results of these from both the application and the FDA -- but the results of these first four studies, two studies evaluating gemifloxacin for seven days, one study evaluating gemifloxacin for five days compared to gemifloxacin seven days, and two non-comparative studies of five days.

The first four -- next slide -- have actually been previously reviewed by the Agency and received non-approval letters. In 2002, a non-approval letter was issued for Studies 9 and 10, the seven-day regimen, and in 2002, Studies 186 and 206, for the five-day regimen, were issued a non-approval letter.

In the letter, the FDA actually wrote that we concluded gemifloxacin is effective in treating a number of infections, including acute bacterial sinusitis, or ABS; however, there was significant concern regarding the cutaneous reactions seen, and therefore, the conclusion was reached that the

benefit did not outweigh the risk for this indication. Next slide.

How efficacy was demonstrated for this indication will be reviewed by both the application and the Agency, and it s summarized briefly in this slide. Next.

What were the safety concerns? As I mentioned, mostly cutaneous reactions, primarily a rash. Overall, the findings were the following. Consistently, there were more frequent rashes seen in the gemifloxacin arms compared to the control arms. And this was across all indications, not just sinusitis.

In addition, there was an increased incidence of rash with increasing duration of therapy. The rash was more common in patients less than 40 years old than patients over the age of 40, and the rash was more common in women than men. In addition, the spectrum ranged from mild to severe rash. Next slide.

Now, this is a figure that s also in your briefing material, and it very briefly summarizes

most of the findings of these rash reactions. Just to quickly orient you, on the Y axis, we have the percent of patients reporting rash, and on the bottom, the left-hand side shows three, five, seven, 10, and 14 days of gemifloxacin therapy; on the right side, the same durations of control therapy.

You can see the rate of rash is related to the duration of therapy. Patients younger than 40 -- these bars -- have a higher incidence than patients over the age of 40, which are these. Again, as you can see, the seven-day regimen does have more rashes than the five-day regimen. Next slide.

So given that that is the safety that we saw for the product overall, how is it that we came to different regulatory conclusions for the different indications? Let me try to summarize our reasoning. We approved the indications of community-acquired pneumonia, CAP, and acute bacterial exacerbation of chronic bronchitis, or ABCB.

These are serious diseases. There s a high mortality and morbidity associated with CAP. There s a risk of patient decompensation with ABCB. In the clinical studies that were submitted, most of the patients were actually over the age of 40, and more than half were male, so despite a higher incidence of rash with gemifloxacin, at the seven-day regimen for CAP and five-day regimen for ABCB, the benefit was judged to exceed the risk.

Furthermore, we brought the applications before the advisory committee in 2003. The committee recommended approval and therefore, Factive was approved for these two indications in April of 2003.

In contrast, for ABS, we issued non-approval letters in 2000 and again in 2002. The potentially seriously morbidity for sinusitis is not clear. In addition, in clinical trials, there were predominately female with a mean age of 40, exactly the population that has the highest incidence of rash.

The rash was greater in the seven-day

regimen compared to the five-day, and these were higher than what was seen in the comparators. Therefore, despite the conclusion that gemifloxacin was effective, the overall recommendation was that the indication not be approved because the risk of adverse events exceeded the benefit for the treatment of this indication.

Nevertheless, Oscient continued to be interested in this indication. We had additional dialogue and in February of 2005, we acknowledged that the Factive applications were submitted before the 2003 advisory committee on acute bacterial sinusitis that was brought before this committee.

We also agreed that judged by the pre-2003 parameters for evaluating efficacy in this indication, the drug was considered effective, and we reiterated our concerns that the rash was more common with gemifloxacin and requested a large comparative safety study to demonstrate convincingly that the incidence of skin reactions, particularly serious reactions, was clinically acceptable and no greater than the comparators.

During that meeting, we actually also commented that we did not grant the organism multi-drug resistant streptococcus pneumonia in the indication of acute bacterial sinusitis, and advised the company that if they were interested in that organism, a placebo controlled trial demonstrating efficacy in ABS secondary to MDRSP would be required.

Let me now turn to the current application before us. This is a new supplement. It was submitted in November of last year, and after some dialogue between the company and FDA, it was accepted for review in March of this year. Next, please.

So as part of review of this application, the FDA has actually been involved in the examination of information submitted for both efficacy and safety, and this includes their review of both new information that has been submitted, as well as previously reviewed information that s contained in this application. This includes information from clinical studies, as well as

post-marketing safety data. Next, please.

So for the review of safety, the application contains clinical trial data from about 8,119 patients who received gemifloxacin. This includes the 6,775 patients whose data was actually reviewed as part of the original application which supported the CAP and ABCB approvals. The application also contains clinical data from 5,242 patients who received comparator drugs, and this is the same number that was included in the original NDA application.

The safety information will be reviewed by Dr. Tierney from the FDA and also by the company. Post-marketing safety information will be reviewed for FDA by Dr. Andy Mosholder. The company will also summarize some interim study reports that they have submitted to the Agency since June 2006.

As far as efficacies, I mentioned there are five clinical studies. Three of these are comparative and all three comparative ABS studies use the non-inferiority trial design. Now, since 2002, there have been a number of public meetings

and workshops where the Agency has discussed non-inferiority trial designs and the necessity for justifying the margin in such studies.

In addition, in October of 2003, an advisory committee took place to discuss the -- it was, in fact, the Anti-Infective Advisory Committee -- to discuss the development of drugs for acute bacterial sinusitis. The committee at the time recommended that superiority trials be used for ABS indications because an appropriate non-inferiority margin couldn t be determined from the available published placebo controlled studies. Next slide.

Now, non-inferiority or similarity trial designs are used quite frequently in development of drugs for infectious diseases, and they re really quite appropriate for diseases whose spontaneous resolution without antimicrobial therapy is low, such as, for example, bacterial meningitis or bacterial pneumonia.

So let me walk you through the reasoning for this. If the clinical success, for example, in an infection, is reproducibly less than 50%, or

even as low as 20%, in a placebo arm, and reproducibly, let s say, 80% or more on an antimicrobial arm, then the difference between 50 and 80 is a 30% benefit of antimicrobial therapy over the spontaneous resolution of the disease, and then a margin that s less than that 30% for the lower bounds of the 95% confidence interval excludes that the effect may due to placebo.

So choosing a margin, for example, of less than 15% or so preserves at least half that benefit. However, if we have a disease with high spontaneous resolution and the clinical success is, let s say, greater than 70% in placebo, and again, 80% for the drug, the benefit is actually less than 10% and a smaller margin may need to be selected.

So how does this relate to acute bacterial sinusitis? What is the benefit of antimicrobials over placebos in that condition? Well, we ve actually reviewed published studies of placebo controlled trials in acute bacterial sinusitis. Seventeen were identified, eight of these have been published since 2000, and Dr. John Powers will

actually present the summary of that review.

Why is this important? Two reasons. The first is we need to do this to determine the benefit of the antimicrobial over placebo, and second, we need to do this because our regulations require that we do that. Next slide.

Let me actually present a couple of slides on the regulations that we need to follow in reviewing and approving products. This is a regulation that defines adequate and well-controlled studies and acute treatment concurrent controlled trials are one type of adequate and well-controlled study.

Now, if the intent of an active treatment concurrent controlled trial is to show similarity of the test and the control drug, then the report of this study should assess the ability of this study to have detected a difference between treatments, because if similarity is shown, that can mean either that both drugs were effective, or that neither was. So one way to do this is that the drugs which should be considered effective in

this study may be judged so by reference to results in previous placebo controlled studies of the active control drug.

What about adequate and well-controlled studies? Well, evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to or is represented to have, is the definition of substantial evidence, and for approval of the product, we need to have substantial evidence within the application.

Therefore, as we review today s application for acute bacterial sinusitis, we need to look at both efficacy and safety. So although Factive was determined to be effective in acute bacterial sinusitis in 2000 and 2002, the indication was turned down due to concerns about the safety profile. So as we examine efficacy in 2006, we need to keep in mind the developments since 2002.

As far as safety, there were concerns regarding the adverse event profile in 2000 and 2002. This led to a non-approval of the indication. So as we examine the safety in 2006, we need to consider all the safety information, both from clinical studies and post-marketing.

So here s a synopsis of this morning s agenda. First, we ll hear presentations from the company, followed by three presentations by FDA. Dr. Powers will discuss sinusitis placebo controlled studies and drug development, Dr. Tierney will summarize the safety and efficacy of Factive for sinusitis, and Dr. Mosholder will review the post-marketing reports.

Actually, then, we will have lunch, and after that, an open public hearing, and then the committee will be asked to debate the following question. So as you listen to the presentations, please keep this question in mind. We ll ask not only for a discussion of it, but also a vote at the end of the day.

The question is: do the safety and

effectiveness data presented demonstrate an acceptable risk-benefit profile for the use of Factive as treatment for patients with acute bacterial sinusitis? If you determine that the risk-benefit supports the use of the product in ABS, then we ll ask if there are special caveats, warnings, or limitations that should be included in the product labeling, and also, we ll ask if there are any specific risk management recommendations that you would like to make for Factive post-approval.

If, on the other hand, you determine that the risk-benefit does not warrant the use of Factive in this indication, then we ll ask if there are other studies or other information that could demonstrate that the benefit of the product outweighs the risk.

With that, I ll turn it back to you, Dr. Edwards, and I just listed a lot of the folks that have helped to make this possible.

DR. EDWARDS: Thank you very much. We re going to move now to the application presentation

by Oscient, and we re actually just a little bit early. The sponsor has asked that because of the amount of information they want to present, that we hold questions until the end of the presentation. So welcome.

DR. ALBRECHT: Dr. Edwards?

DR. EDWARDS: Yes?

DR. ALBRECHT: May I ask that we recognize two other colleagues who ve joined us? Could you ask them to introduce themselves? Drs. Temple and O Neill have joined us.

DR. EDWARDS: Thank you.

DR. TEMPLE: I m Bob Temple. I m Director of the Office of Medical Policy in Cedar.

DR. O NEILL: I m Bob O Neill. I m the Director of the Office of Biostatistics in Cedar.

DR. EDWARDS: Thank you very much. Welcome. Please.

DR. PATOU: Good morning, members of the advisory committee and the FDA. I m Gary Patou. I led the development of gemifloxacin during its Phase I through III clinical trials, and I ll lead

you through today s presentations on gemifloxacin for the treatment of acute bacterial sinusitis, or ABS.

We ll discuss two primary issues with you today. First, we ll explain why, with controversy over the role of antibiotics in this condition, and multiple FDA-approved agents, why we need gemifloxacin for the treatment of ABS.

We ll show data that demonstrate gemifloxacin would be an important therapeutic option for the treatment of ABS, particularly where the risk of infection by resistant organisms is of concern.

The data demonstrate that gemifloxacin has a highly favorable PK/PD profile and was very effective in clinical trials in only five days of therapy. We ll also explain why a short course of therapy is important.

The second issue we ll cover is gemifloxacin associated rash. We ll discuss the safety profile of the drug, particularly in terms of rash, and we ll compare gemifloxacin s adverse

effects to those of other currently marketed antibiotics for ABS.

The consistency of the safety experience with gemifloxacin, through multiple studies and multiple databases, will be a constant theme in our presentations today. We believe that when the efficacy and safety of gemifloxacin for this indication are placed into context, a favorable risk-benefit profile emerges.

To briefly review gemifloxacin s recent regulatory history, three years ago, this advisory committee recommended FDA approval of gemifloxacin for acute bacterial exacerbations of chronic bronchitis, ABCB, and mild to moderate community acquired pneumonia, or CAP. The FDA approved the drug for those indications one month later.

In November, 2005, the sponsor filed a supplemental NDA For five days of therapy for CAP and five days for ABS. We re here today to discuss ABS. We come to you with many times the patient exposures that we had in 2003, and two years experience marketing gemifloxacin.

The ABS clinical trial program was conducted in state-of-the-art trials, which meet all current FDA guidelines for the development of drugs for the treatment of acute bacterial sinusitis. The FDA has not issued any new guidelines to date, and recently, there have been four ABS approvals based upon programs conducted according to the existing guidelines, mainly studies of non-inferiority design.

The gemifloxacin clinical trials met all of their primary and secondary end points, and the FDA has communicated on previous occasions that gemifloxacin is efficacious in the treatment of ABS. We will present data from the entire gemifloxacin clinical development program, and I ll describe that program for you now.

First, the clinical trial database from the 2002 NDA of 6,775 patients and from Study 344, an intense examination of rash in more than a thousand healthy women. Second, three further clinical trials, including an additional five-day ABS study.

These three additional studies were submitted to the FDA in the 2005 sNDA. Importantly, they increased the five-day ABS database by 40%, bringing the total number of patients in gemifloxacin clinical trials up to 8,119.

We will also show data from the Phase IV FORCE study, which focuses on drug safety and the Prescribing Use study. Both of these were post-marketing promises made and kept to the FDA. Scheduled interim annual reports from these studies were submitted to the FDA in June of 2005 and 2006.

Finally, we will discuss our U.S. post-marketing database of 760,000 patient exposures. When you include 200,000 ex-U.S. post-marketing patient exposures, we have nearly a million patient exposures to gemifloxacin. The FDA s briefing book limits its analysis to the 2002 NDA population of 6,775 and the post-marketing surveillance reports.

While we understand that the FDA has not fully reviewed all of the data that you see on the screen, the sponsor has analyzed the data and

believes these data can help the committee address the FDA s concerns about gemifloxacin.

Before I review the agenda for the rest of our presentation, I d like to emphasize that acute bacterial sinusitis can cause significant morbidity. To quote ABS expert Dr. Jack Wortney (phonetic), despite the fact that true acute bacterial sinusitis may occur in only a small percentage of cases of viral sinusitis, it remains a serious health issue.

Respiratory tract infections are the number-one reason patients visit doctors offices, and sinusitis is the most common respiratory tract infection in adults. In fact, there are 800,000,000 cases of rhinosinusitis per year, and of these, between five and 20 million cases are believed to be bacterial; that is, ABS.

These patients deserve the best possible treatment, and with any infectious disease, the implications of treatment go far beyond the individual patient. We should not only seek to better define the subset of ABS patients that

benefit from antibiotics, we should also use agents that are least likely to cause resistance, to minimize the burden on public health.

Now, here is our agenda for the rest of today s presentations. First, Dr. Donald Low, Chief of Microbiology at the Mt. Sinai Hospital in Toronto, Professor of Medicine at the University of Toronto, and Medical Director at the Ontario Public Health Laboratory, will talk to us about the problems of emerging antimicrobial resistance in streptococcus pneumonia and possible solutions.

Dr. Low is widely published on streptococcus pneumonia drug resistance, and is on the CLSI committee that determines antibiotic break points for North America.

Dr. B.J. Ferguson is Director of the Division of Sino Nasal Disorders and Allergy in the Department of Otolaryngology, Head and Neck Surgery at the University of Pittsburgh School of Medicine. She will describe the efficacy data from the ABS clinical trial program.

Dr. Neil Shear, Professor of Dermatology

at the University of Toronto, will review the cutaneous data. Dr. Shear runs a clinic for patients with cutaneous drug reactions and is at the forefront of research into the cutaneous effects of drugs.

Dr. Paul Waymack, former burn and transplant surgeon at Shriners Burns Institute in Galveston, Texas and former FDA Medical Officer, will present the safety data on gemifloxacin, and I will then discuss risk-benefit and our risk minimization program.

As you see on the screen, we have five additional experts with us today to answer any additional questions that you may have. Now, I ll turn the podium over to Dr. Low. Thank you.

DR. LOW: Thanks very much, Gary. My interests have been in the epidemiology and mechanisms of antimicrobial resistance and how it impacts patient care and clinical outcomes. In fact, I was here in 2003, presented the committee the importance of choosing the right antibiotic for the treatment of acute exacerbations of chronic

bronchitis and community acquired pneumonia in order to minimize the development and dissemination of resistance.

So today, I m going to argue that, in fact, it s just as important that if we re using an antibiotic to treat acute bacterial sinusitis, that we use the right antibiotic, even if it s for a much less severe infection, like acute bacterial sinusitis.

Now, I m going to focus on the pneumococcus, because it s clearly the most important bacterial cause of respiratory tract infections, the one associated with the greatest morbidity and mortality. What I d like to show you to start off with is a schematic which describes how resistance emerges in respiratory pathogens, particularly in the nasopharynx.

It s important to recognize that acute bacterial respiratory tract infections, whether it s otitis media, sinusitis, community acquired pneumonia, that the bacteria originate in the nasopharynx. The nasopharynx is a reservoir for

bacteria, including pneumococci, even in healthy individuals.

When somebody develops a viral sinus infection, this creates an environment conducive to colonization with bacteria, including pneumococci, and sometimes resulting in bacterial infection, acute bacterial sinusitis.

Now, if an antibiotic is decided to be used, the goal of therapy is to eradicate that bacteria without creating antibiotic resistance. However, using a long-acting drug or a marginally effective drug, that can create an environment that selects for resistance. In some case, the same resistant bacteria can, once again, cause acute bacterial sinusitis, they can cause community acquired pneumonia, and probably even more importantly is they can be transferred from person to person; that is, a spread of resistance.

During the 1990s, as you re aware, we saw the rapid emergence of betalactam resistance to the pneumococcus from less than 2% in the 1980s to greater than 15% by 2001. During the same time

period, we saw the emergence of macrolide resistance in the pneumococci.

In Dorn s recent U.S. surveillance study publishes last year in Clinical Infectious Disease, he noted a similar, although not as dramatic, increase in Floroquinolone resistance to pneumococci. He also noted a quite marked dramatic increase in the number of isolets with first step mutations. This is a marker for impending resistance, and when you see such a dramatic increase, you have to be concerned that resistance may soon follow.

Dorn also showed in that study a disturbing number; that is, the number of multi-drug resistant streptococcus pneumonia at 25%. This emphasizes the need for agents such as gemifloxacin that are approved for the treatment of patients infected with such isolets.

Now, in Canada, we ve had in place a prospective surveillance program since the early 1990s, not only to monitor resistance rates, but to look at the factors that are actually driving

resistance. This network collects isolets from 65 different laboratories across Canada, and what we ve found is that long-acting drugs, and those with marginal activity, alter resistance rates.

Here, we see the progressive increase in the prevalence of macrolide resistance in Canada in association with a decrease in the use of short-acting macrolides, like erythromycin, and an increase in the use of long-acting macrolides, azithromycin and clarithromycin.

Now, these same observations have been made by a number of investigators in different countries. The explanation, I think, appears to be related to the fact that long-acting macrolides were remaining in the mucosa at sub-optimal concentrations, therefore creating an environment that selects for macrolide resistance.

These Canadian data show Floroquinolone resistance in pneumococci increasing rapidly during the 1990s and at the turn of the century, but then, since 2002, an actual decrease in resistance rates.

So why the decrease? We believe the

decrease was caused by the introduction and widespread use of floroquinolones with optimal activity against pneumococci; that is, gadifloxacin and moxifloxacin.

The green line shows you the decreasing use of Ciprofloxcin, a floroquinolone with less than optimal activity against the pneumococci; the blue line shows you levafloxacin use, a floroquinolone with marginal pneumococcal activity; and the orange line shows you the combined use of gadifloxacin and moxifloxacin, two floroquinolones with optimal pneumococcal activity.

Unfortunately, gadifloxacin is no longer available, leaving only moxifloxacin as a floroquinolone with optimal pneumococcal activity. Clearly, we need more choices within this class. Specifically, we need an antibiotic that is highly active against pneumococci, such as gemifloxacin.

PK/PD parameters support the observations that more active quinolones can minimize the emergence of resistance. Two important parameters. One, the AUC/MIC ratio; that is, the area under the

concentration curve divided by the MIC, and the peak plasma, or CMAX/MIC ratio.

Now, the AUC/MIC ratio that has been associated with bacterial eradication in clinical cures has been one greater than 30, and currently, the respiratory floroquinolones achieve this ratio.

In an important paper published in JAMA in 1998 by Preston and Drusano, they found that favorable clinical and microbiological outcomes were most likely to occur if a CMAX/MIC ratio of 12 was achieved. As shown here on the right-hand side, gemifloxacin is the only floroquinolone that meets these criteria.

Gemifloxacin has a unique ability to bind equally and effectively to both of the targets that are essential for DNA replication in bacteria, at concentrations that are achievable in the pt. This is reflected in its ability to kill quinolone-resistant pneumococci. On this slide are the results of time kill studies using concentrations equivalent to free unbound drug that would be found in a patient. Only gemifloxacin,

represented by the yellow line with circles, was bactericidal.

Based on its excellent PK/PD parameters and its dual targeting ability, we believe that gemifloxacin can limit the development and dissemination of pneumococcal resistance to the floroquinolone class.

Low potential for resistance induction is one of the six key criteria outlined by Sandy (phonetic) and Gwaltney for the treatment of acute bacterial sinusitis. The other criteria include the ability to penetrate tissue rapidly, to be of the appropriate spectrum of activity, to be rapidly bactericidal, to have a half life appropriate for once a day therapy, and short-term dosing.

So how does gemifloxacin stack up against these recommendations? Gemifloxacin meets all the criteria for the ideal drug for ABS. As a class of floroquinolones, they all rapidly penetrate tissue, they are rapidly bactericidal, and they have an excellent activity against the pathogens causing ABS.

In addition, gemifloxacin has a half life of eight hours, which allows for convenient once-a-day dosing; its five-day course of therapy minimizes the exposure of the pathogen to the antibiotics; and finally, we have shown here using the most active floroquinolone reduces the potential for resistance induction.

Thank you for your attention, and I ll turn the podium over to Dr. B.J. Ferguson, who will present the efficacy data for gemifloxacin in ABS.

DR. FERGUSON: Thank you, Dr. Low. Good morning. I m B.J. Ferguson. I ve been on the faculty of the Department of Otolaryngology at the University of Pittsburgh Medical Center for almost 14 years. I treat predominately patients who have sino nasal problems, and I do believe we need more effective antibiotics for the treatment of acute bacterial sinusitis. We need antibiotics that are easy for our patients to comply with, antibiotics that work when other antibiotics have failed, antibiotics that work when patients are truly ill. We need antibiotics that are responsible to the

community and can reduce the spread of resistance.

When patients have sinusitis, they suffer. They suffer from facial pain and pressure, purulent drainage, nasal blockage, impaired sleep, fatigue, impaired quality of life, and impaired productivity, and sometimes, they suffer from rare complications of intracranial infection, orbital abscess, meningitis, and sometimes, they suffer from persistent sinus disease.

It is up to the treating physician to accurately diagnose and treat the truly ill patient with an effective antibiotic. Today, I ll present data that will show you why gemifloxacin belongs in that group of oral antibiotics most effective for ABS.

While there are many antibiotics that are indicated for ABS, the emergence of resistant bacteria has rendered many of these considerably less effective. In the case of strep pneumoniae, the resistance is now to multiple classes of antibiotics, multiple drug resistant strep pneumoniae, MDRSP, and a number of such organisms

were isolated from patients in the gemifloxacin program.

This is a table modified from Dr. Jack Gwaltney s chapter on sinusitis in the 2005 Mandell s Infectious textbook. I have added telithromycin and the five-day indication for levafloxacin. This reflects the most effective antibiotics currently for acute bacterial sinusitis.

When we are dealing with highly resistant strep pneumoniae, which you heard from Dr. Low s presentation is increasingly common, there are only three classes of antibiotics that remain effective: high-dose amoxicillin, telithromycin, and the floroquinolone class.

Today, I ll share data with you that demonstrates gemifloxacin s efficacy with a five-day course of therapy. The gemifloxacin clinical development program started off as a seven-day program, comparing two effective antibiotics approved for the indication.

During this period of time, shorter

courses of therapy were being studied and some were subsequently approved. A shorter course is easier for the patient to comply with fully and there is less pressure for the development of resistance. So the sponsor moved the gemifloxacin clinical program from seven days to five days, and as you ll note in your briefing book, there was a lower incidence of rash.

The gemifloxacin program was extensive, consisting of five trials of more than 1,800 patients, and as we ll see, all of the studies not only met, but exceeded the preset non-inferiority boundaries. The studies also employed the gold standard for evaluating bacteriology in sinusitis, maxillary sinus taps.

Sinus tap data was collected on more than 1,200 patients. Of those, nearly 900 patients were on gemifloxacin. (inaudible), and these criteria were more rigorous than those developed by the Task Force on Rhinosinusitis sponsored by the American Academy of Otolaryngology Head and Neck Surgery for diagnosing rhinosinusitis a decade ago.

Patients in the comparator trials had to have at least seven days, and not more than 28 days of symptoms. They all had nasal purulence by exam. They all had radiographic evidence of acute bacterial sinusitis by either total opacification, or an air-fluid level.

Note, patients with only mucosal thickening were excluded. This is a lesser criteria. They all had to have major and minor criteria established by the American Academy of Otolaryngology. Patients were excluded in all the studies if they had been on antibiotics in the last seven to 14 days, had nasal polyps distal to the middle turbinate, or had had sinus surgery within the last six months.

In the next two slides, you ll see that these are patients who had a constellation of symptoms. 95% of the patients with symptoms for at least three days, but less than seven, had two or more major criteria, and a multitude of minor criteria. You see here that the patients who had seven days of symptoms or more had a similar

pattern.

The first two studies were randomized, double blind comparator studies, seven days of gemifloxacin against 10 days of two approved comparators for ABS, cefuroxime or trovafloxacin. At the time of these studies, trovafloxacin was considered to be one of the most effective antibiotics for respiratory pathogens.

In these studies, gemifloxacin was non-inferior to its comparators. In addition, a third bridging study was conducted comparing seven days of gemifloxacin to five days of gemifloxacin. I was an investigator and the primary author on this study, which was published in 2002. Finally, two open-label maxillary sinus tap studies were done, using five days of gemifloxacin.

Here, we see a summary of the clinical success rate in the controlled trials. We see the point estimates range between 87 and 91%, and are similar with gemi and the comparators. These were large studies with more than 150 subjects per study arm enrolled in each of these trials.

As you can see graphically, all of these controlled studies achieved a non-inferiority boundary of less than 10% based on the primary analysis population, even though the studies were designed to meet the minus 15% non-inferiority guidelines at the time. The results for the intent-to-treat population were similar, except for a minus 10.6% boundary in the ITT population of Study 009.

Now, let s look at the open-label studies in which gemifloxacin was given for five days. What you see is a similar success rate of gemi of 87 to 90% in the per-protocol population at test-of-cure, and this is in line with the clinical success rate we ve seen in the controlled studies.

So now that we ve established the clinical efficacy of gemifloxacin, what I really think is important is to look at the bacteriological efficacy of the drug, because it s in the bacteriologically evaluable patients that we can truly expect to best determine in antibiotics efficacy.

Here, we see that the bacteriologically positive patients in Study 009, in which they had seven days of gemifloxacin, are compared to those who received cefuroxime for 10 days. What we see is that about half of the patients who were tapped had a bacterial pathogen, and this is standard for these studies.

The overall presumed bacterial eradication for gemifloxacin for seven days was 92.57%, compared to 94% for cefuroxime, but shown on this slide are the clinical and presumed bacteriological success for the specific bacterial isolets, and gemifloxacin achieved 100% clinical and presumed bacteriological success in the 14 patients infected with MDRSP.

Now, this is noteworthy because when you look at the cefuroxime arm, cefuroxime was only 80% effective, and the three failures were organisms which were resistant to cefuroxime. I think this is a tie between the bacteriological efficacy of the drug and the clinical efficacy of the drug, and it shows that it s important to have a drug that

provides coverage for multi-resistant organisms.

Let s move on to comparing the bacteriology from the seven-day gemi trial to the two open-label five-day studies. You can see that there s a similar distribution of the major pathogens and a similar clinical and bacteriological success rate. In the two open-label studies, we had 24 multi-drug resistant strep pneumoniaes. Gemifloxacin achieved 100% clinical and presumed bacteriological efficacy in this group.

Now, these open-label studies were not placebo controlled, they were maxillary sinus tap data, and this is the gold standard for determining bacteriology in ABS. What we see is gemifloxacin is effective when patients have a bacterial disease, and it s very effective when they have pathogens that we worry quite a bit about, the multi-drug resistant strep pneumoniae.

On a final note, in 2004, the Sinus and Allergy Health Partnership ranked floroquinolones as the most effective antibiotics for acute

bacterial sinusitis.

Gemifloxacin is not on this list because it does not have an FDA approval for sinusitis, but its in vitro PK/PD characteristics demonstrate that it is the most effective of the floroquinolones for strep pneumoniae. If gemifloxacin is approved for ABS, it would belong at the top of this list.

Now, I d like to turn the presentation over to Dr. Neil Shear, who will discuss gemifloxacin s cutaneous safety profile.

DR. SHEAR: Good morning. Thank you very much. I m Neil Shear and I m here to talk about the cutaneous effects of gemifloxacin. My practice is in dermatology and clinical pharmacology, and as Gary mentioned, in drug safety, for over 20 years. I ve been working on the pathophysiology and the clinical management of drug reactions, in the skin and systemically.

In March, 2003, I shared with this committee data on gemifloxacin rash, including a study conducted by this sponsor at the FDA s request to specifically characterize the rash, and

this is called Study 344, and we ll come back to it several times, and it s in your notes, as well.

Today, we have a great deal of additional data, however, which I have analyzed so we can continue to understand this rash. This is what I m going to look at in the presentation. I really want to try and understand what is meant when we just say the rash ; what are we talking about? And there s many different components. So we need to look at the epidemiology: what types of rash are we seeing, how many, and how severe are these rashes?

We also want to go back to Study 344 to understand the pathophysiology. We want to assess risk, so we re going to look at covariants and what factors should be considered when trying to understand risk. We ll look at the potential for cross and subclinical sensitization, an issue that had been raised.

In other words, if a person had had a rash while on gemifloxacin, would they develop a rash from another quinolone subsequently, and in a

subclinical sensitization setting, if they did not have a rash on gemifloxacin, but were re-exposed to that same drug, would they get a rash?

The most important consideration was the potential for cutaneous conditions, like Stevens-Johnson and toxic epidermal necrolysis.

I ll cover the issues outlined in this slide, and I ll be pulling data from the following studies and populations: the clinical studies of gemifloxacin versus comparators, including the ABS five-day trials; Study 344, the study to look at the rash; two Phase IV studies, FORCE and Prescribing Use; and particularly, from the post-marketing adverse event reports from the AERS database.

I will present data from all of these studies and populations and analyze them according to the information needs that I summarized at the opening to try and understand what is the rash, what does this mean? I ll begin with the covariants of rash incidents and data from the clinical trials.

Duration of therapy was one of the most important covariants of rash discovered in the clinical trials. Here, we can compare the incidents of rash in the five-day ABS population with the seven-day ABS group, the full safety population and comparators.

You can see the effect of the shorter duration of therapy and incidents of rash, and in serious adverse events, in rash leading to withdrawals. We can see here that duration of therapy really does make a difference; the shorter the duration, especially at five days, the less rash we see.

Here, we re looking at the impact of age on the incidents of rash. Age is a covariant, but when we look at duration of therapy in association with age, a shorter duration of therapy produces a lower incidence of rash, no matter the age of the patient. In the shorter duration, five days, we see the rates of rash in both the over 40 and under 40 groups are actually quite similar.

The other important covariant identified

in our analysis of the clinical trial data was gender. You see a difference between the genders, particularly in the longer duration of therapy in women under 40, but in the five-day population, we see that the difference narrows considerably.

Supporting this effect of duration of therapy on rash frequency is data from one of the Phase IV studies, the FORCE study, an ongoing trial designed to study the safety of gemifloxacin. As we see in a five-day duration of therapy for bronchitis, the rash prevalence was 1.3%. There were no SAEs of rash in any of the groups, and rash leading to withdrawal was also low, at less than 1% in all groups.

When you consider age and gender, we see the same impact of length of therapy on the rate of rash, albeit with a smaller number of women under 40 in the group. The rate of rash in five days of therapy is 1.3% for all patients, 1.8% for all women, and 2.8% for women under 40.

So we ve established that both gender and age influence the rate of rash, but become less

important as predictors of rash when the duration of therapy is down to five days. The most important covariant of rash prevalence is the duration of therapy.

Now, let s go to Study 344 to answer some other questions, especially on pathophysiology. Study 344 was a unique study. It was conducted to help us understand the clinical nature of the rash, not to determine rash prevalence. I was involved in that trial and it was the most comprehensive study of a simple exanthem that I ve ever seen, I m sure that has ever existed and may well ever be.

We purposely recruited a population that we knew from the clinical studies would have a higher incidence of rash in a longer duration of therapy, so it was young women who were being treated for 10 days to ensure an adequate sample so as to study the rash. Our goals were three fold: one, to characterize the rash both clinically and pathologically; two, to see if there would be cross-sensitization; and three, to determine the potential for a subclinical sensitization. In

essence, we really wanted to find out if the rash was just a rash, a typical drug-induced exanthem, or was it anything more than that.

I m showing this slide as an overview of the flow of Study 344. Healthy subjects in a Phase I setting were randomized at 10 days of gemifloxacin or ciprofloxcin. This allowed us to find rashes and characterize them clinically and pathologically. Then, after a washout (phonetic) period, subjects were exposed in order to investigate the sensitization questions in the Part B of the study. Each arm of Part B was placebo controlled.

Now, let s look at the morphology of the rash, an important characteristic. Study 344 is extremely valuable because we were able to have dermatologists look at every patient who had a rash, they were seen every day, and we have photographs of all the rashes.

Now, on the left is an example of the typical rash seen with gemifloxacin, and I reviewed lots and lots of rashes. Mostly what you see is

this kind of rash. You can t use this for teaching. It doesn t show much.

On the right is with the worst rash. This is a typical drug exanthem. I know I ve certainly seen worse with many of the drugs we used, like betalactams, and this was the worst-looking one that we have seen, but I ll show you some others.

Here are some of the rashes that investigators called severe. Now, the definition of severe in this study was that it impacted on their daily activities and would not allow them to conduct them. As in other clinical studies, this was not a measure of seriousness.

As you can see from these photos, there are no morphological features indicating anything more than a mild to moderate exanthem. This was a typical, non-serious, self-limited drug rash. And we looked for vasculitis clinically and pathologically, (inaudible) regions for pustular changes, for mucosal lesions -- especially, the hemorrhagic crusting that is characteristic of Stevens-Johnson Syndrome, and we did not see any of

these morphological features in this study.

In addition to our ability to take photos of all patients with rash, we were also able to perform biopsies on the patients. Biopsies were taken from both affected -- so the rash itself -- and unaffected, or clinically normal-looking skin. Now, these biopsies generated 10,000 slides for routine histology, immunofluorescence, and immunophenotyping of any cellular infiltrate.

In unaffected skin of subjects who had a rash, so in the normal-looking skin, we saw nothing other than normal skin. In the skin where there was a rash, there was a very mild infiltrate. In the immunohistochemistry, we saw that the few cells that were there, we could see they were round blood vessels, and that they were T-cells, and they were CD4 positive.

Now, that s actually a reassuring sign, because in blistering rashes, you tend to see an increase and more predominance of the CD8 positive cells. So what we were seeing was a very benign and typical exanthem picture. There is no hint of

the features of the blistering diseases, nor vasculitis, at any of the levels of the immunofluorescence, the immunophenotyping, or frankly, just the histology. We found nothing whatsoever, other than the typical picture of a drug rash.

Now that we ve established the benign clinical and pathological nature of the rash, we ll turn our attention to the potential for gemifloxacin to cause cross and/or subclinical sensitization. Of the women who had a rash on gemifloxacin, and then received ciprofloxcin in Part B of the study, about 6% developed a rash. Of those who had a rash on the gemifloxacin arm and then received placebo, so the comparator group to this, 3.5% developed a rash.

So we determined that cross-sensitization, if it exists, was at a low rate, and it was interesting to note that in the patients who developed a rash in Part B on ciprofloxcin, this was very characteristic of the ciprofloxcin rash. It came earlier on, was quite mild, and was the

type of rash that we saw in the right-hand part where people just got ciprofloxcin the beginning.

So the gemi rash was the gemi rash, and in the excess, the 2% of the people who got a rash were seeing a cipro rash. We saw no subclinical sensitization. The people who did not get a rash on gemifloxacin and were reexposed to gemifloxacin about a month later had a rash similar to placebo.

Now, we also looked at cross and subclinical sensitization in the Phase IV Prescribing Use study. This study uses an HMO database to analyze prescribing patterns in the use of gemifloxacin in the United States. Here, we see consistency with Study 344, first looking at cross-sensitization. Of the 147 patients who developed a rash on gemifloxacin, 21 of them were then exposed to another quinolone, and only one developed a rash.

Notably, four of the 147 patients with an initial rash were retreated with gemifloxacin, and none of these four had an identified rash.

Next, we ll look at subclinical

sensitization. Of 4,766 patients who did not develop a rash on gemifloxacin, 244 received another course of gemifloxacin and only one was reported to have a rash. Of additional interest, 738 of the total patients without an additional rash were then exposed to another quinolone. Seven, or just under 1%, developed a rash.

So again, we see that the risk of cross-sensitization is low, and there appears to be no risk of subclinical sensitization.

Now, to study the nature of the observed rash, here are the well-established characteristics that we look for when trying to distinguish a serious from a non-serious rash or exanthem. First, we examine all of the serious adverse events, then we review the descriptions of the rash morphologies, analyze the data for important features, like oral mucosa involvement or skin detachment.

We look for evidence of concomitant fever and other organ involvement, including joint, liver, or kidney related signs or symptoms.

Because the presence of these factors may indicate a more serious consequence, with systemic drug-induced illnesses, like serum sickness like reaction, hypersensitivity syndrome, which has fever, rash, and hepatitis or nephritis, Stevens-Johnson or toxic epidermal necrolysis, where there s extensive blistering of the skin and the mucosa.

Most of the rashes in the clinical trials in the gemifloxacin group were judged to be of mild to moderate intensity. Reports of severe rash in the five-day ABS group was comparable to comparator at only 0.2%. We made this same observation in 344 and in the FORCE trial. Most of the rashes were of mild to moderate intensity.

Okay. I got mixed up on slides. Here we go. Okay. You know what? Go back a slide. I should ve looked, and I missed a slide. I m sorry. Serious adverse events of rash were rare in all of the trials. In the clinical trials, they occurred in 0.1% of patients or less, and in morphology, they were all simple.

There was one case with mycoplasma pneumonia and (inaudible), but it was considered not to be due to the drug. There was no systemic symptoms, no other organ involvement, and no serious adverse events. Most of the rashes in the clinical trials in the gemifloxacin group were judged to be mild to moderate intensity, as you heard before.

Reports of severe rash in the five-day ABS group was compared to the comparator at only 0.2%. We made the same observation in 344 and in the FORCE trial, and most of the rashes were of mild to moderate intensity.

Rash does not appear to be associated with the signs and symptoms of systemic involvement. In the clinical trials, systemic signs were looked at in terms of laboratory values and assessments using eosinophilia, abnormal liver function tests. Thirty- nine, or 0.48% of patients met the systemic criteria of concern, and only two of these had developed a rash. Neither of these, though, had a serious systemic illness.

In 344, when we were looking for rash, we saw no association of rash with the eosinophilia, or liver involvement. There were six cases of fever. One was associated with lymphadenopathy. But these six cases had no associated systemic symptoms or lab abnormalities, and these were looked for intensely, so none were a true hypersensitivity syndrome.

There were no cases in 344 or FORCE of hypersensitivity syndrome reaction or Stevens-Johnson Syndrome, but there was one case of angiodema, which actually came on early on in the study, quickly cleared, and the patient actually continued and finished their course of gemifloxacin.

We now turn to the postmarking adverse event reports from the AERS database. We have reviewed all 706 MedWatch reports related to the skin to look for life-threatening cutaneous reactions. Whenever possible, we ve applied the same algorithm used to analyze the other databases.

Importantly, our methodology was as

rigorous as that employed in the other analyses of gemifloxacin data. We searched the database for serious adverse events, rash morphology, fever, other organ involvement, and the eosinophilian association with rash.

Now, the FDA has raised the issue of other features that could be seen in the serious adverse event reports, and I ll discuss these also. In the briefing book, I want to make the point, there are good definitions of erythema multiforme and Stevens-Johnson, but I do not agree that erythema multiforme is a precursor, or will be become Stevens-Johnson Syndrome.

This is now well understood in the literature that these are two different diseases. Clinically, they share some pathological features, but clinically, they are two different diseases with different sets of causes and different outcomes. I think the analysis of the reports here will actually support that.

Also, skin exfoliation is not necessarily a serious sign. This is the sloughing or peeling

of the superficial layer of the epidermis. It can look dramatic after an inflammatory reaction, and in fact, it s a classical post-measles sign, but it is not necessarily medically important. Again, we ll review the case summaries.

There were 706 reports of rash and 31 SAEs, which may be slightly higher than the FDA total, but this is the number that I reviewed. This did include all the ones that the FDA had mentioned, and it includes three possible cases of Stevens-Johnson Syndrome, so it will be important to look at those.

There were also cases of potential concern involving the skin, and I reviewed those in detail. There were 31 SAEs to review and 14 were simple exanthems, many of which were considered mild to moderate, and one actually was extensive. Of six reports of fever and rash in AERS, none had the usual criteria for hypersensitivity syndrome. They just had fever and rash, but no systemic involvement. There was another case reported with photosensitivity. It was on the face. It was not

severe.

In three cases, Stevens-Johnson was reported to MedWatch, and again, we ll talk about that in a minute. The case of vasculitis was complex, and it wasn t biopsied to prove the diagnosis. I don t know what else to say about that case. It didn t sound Clinically like a vasculitis, but the patient was a very complex patient. There was a death from hemophagocytic syndrome, which was considered by all to not be associated with the drug.

Now, I wanted to be comprehensive in my review of the MedWatch reports, so we looked for cases that might indicate a signal for cutaneous reactions with a systemic component, and here s what we found. Seven other cases had fever associated with rash, and yet again, none of these were hypersensitivity syndrome.

Six had rash and joint symptoms, but none of these fit a serum sickness like reaction, because none of these had fever, just rash and joint involvement. I don t want to undervalue the

data. This is what it showed. We did not get a clear sign of any cases of a systemic disease.

The next cases of raised liver enzymes and the eosinophilia were single cases that actually had lab values that were not much different than normal variation. Other than the three cases that were reported SJS, the skin exfoliation reports were nothing more than peeling of superficial skin, not epidermal detachment, as one would see with a more severe blistering reaction.

Mucosal findings were also quite minimal, and the mucosal findings of Stevens-Johnson are not trivial. These are people who had small, perhaps a single blister in their mouth. Finally, there were three cases of erythema multiforme. Now, two of these had what sounded like the typical acral target lesions that were not systemically ill, and another one had what sounded to be an annular urticaria as it formed confluent plaques, which is quite characteristic of types of (inaudible) urticaria, and have nothing to do with erythema multiforme.

Now, let s talk about the potential Stevens-Johnson cases. There were three cases identified as possible Stevens-Johnson Syndrome in MedWatch. The first was a 67-year-old woman who developed a rash after being on levafloxacin for four days for sinusitis, and then took three to four days of gemifloxacin.

After therapy, the patient developed a diffuse rash with what were called mucosal and vaginal lesions. She was admitted to the hospital and put on corticosteroids. The emergency room physician reported the rash as consistent with SJS. The patient was discharged from the hospital after two to three days.

Normally, patients with true SJS or TEN are hospitalized for more than that, perhaps a week or more, and the rapid onset after therapy and the resolution that was so rapid of the mucosal lesions is really not convincing or really consistent with SJS. I respect the report, but it s hard to call this Stevens-Johnson.

The second case involved an 18-year-old

female who was prescribed gemifloxacin for strep throat. Itching started the day after taking the first dose of gemifloxacin. She then developed what were called hives and was admitted to the hospital, treated with steroids, and continued on Benadryl. Her uncle reported a possible SJS, but this was not medically confirmed as far as he was aware, and these were the terms he used.

The patient was hospitalized for seven days. There were no reports of skin blistering there, and the report is indirect and lacks medical support, but it s a possible case of SJS by virtue of it being a report.

The third case involves a patient who developed what was called a severe rash, and after starting therapy with gemifloxacin. No information was provided on dose, date, duration, condition being treated, patient s gender, the age, medical history, and concomitant medications.

The reporting physician described the rash as Not macular papular, not benign, and like Stevens-Johnson Syndrome. Patient was admitted to

the hospital, treated with epinephrine and other medications -- epinephrine not being a drug we would use for Stevens-Johnson. I m not sure what that was.

So again, we have a case that really isn t complete, but we do respect it as a case that was reported. We have perhaps two, maybe three cases of potential Stevens-Johnson Syndrome, none, of course, that are considered definite, and I don t think we disagree on that.

This is a graph now from the post-marketing data, because I want to go back and talk about the exanthem and the importance of really going back to look at the data in detail. This is from the post-marketing numbers, and this shows the time of onset of the rash, the typical gemi rash, in relation to first day of drug. So you start the drug and for however long you take it, we take a look to see when you start getting the rash.

Now, you can see there s two clusters. There s an early rise in rash rate in the first

three days of treatment and a later one starting around days six and seven. Now, I ve added the results from the clinical trials. The post-marketing pattern is strikingly similar to what we saw in our clinical trials. You see that early rise, and then you see the second rise of two rashes.

Now, if you lump the timing together, it can result in an average that isn t meaningful. So if you look at a one-day and a seven-day, you can come up with a four-day median, but that really doesn t make sense. We re seeing two different rashes here at two different times.

So in summary, I ve looked at the original clinical trial database for gemifloxacin, and Study 344, an intense trial to characterize rash with gemifloxacin, and the Phase IV studies and additional post-marketing data. I ve looked at predictors for serious cutaneous reactions, specifically Stevens-Johnson and toxic epidermal necrolysis, and all cutaneous findings are consistent with my original conclusions in 2003,

but we have much more data.

The rash that occurs with gemifloxacin as used as a five-day course for ABS occurs in approximately 2.6% of all patients. The rash is a benign, exanthematous rash. Now, there were some cases of attention (phonetic), and I don t want to minimize those. There were cases of rash and fever, but they had no systemic disease.

There were cases of joint swelling or pain with rash, but no fever, so no cases of serum sickness like reaction. There may be two, maybe three, possible cases of SJS, but no reports of toxic epidermal necrolysis, and certainly, no reports of definite Stevens-Johnson Syndrome.

I see evidence also of low cross reactivity and low subclinical sensitivity in all of the studies and the data that we have, and it s substantial. So we have much more data now, three years later, and I continue to be reassured about the nature of this rash and the cutaneous safety of this drug.

I will now turn the podium over to Paul

Waymack, who will discuss the overall safety of gemifloxacin.

DR. WAYMACK: Thank you, and good morning. Gemifloxacin has side effects, as do all other drugs, and thus, as is generally the case, the critical questions become how does its side effects profile compare to its efficacy and how does its side effects profile compare to the profile of other drugs approved for the same indication?

You ve already heard described gemifloxacin s efficacy. I would now like to describe its safety profile and compare it first to the safety profile of the active comparators used in the clinical trials.

As Dr. Patou mentioned, the sponsor s experience ha grown a great deal since the approval for the CAP and the ABCB indications. I m going to describe and walk through the multiple new sets of safety data. Let me say that the bulk of the ABS data was contained in the database that was presented in 2003 and reviewed by you at that time. However, we now have an additional 1,344 patients,

bringing the total population to 8,119.

As I go through my presentation, I will first describe the entire database, and then I will break out the five-day ABS sub-population and compare it to the total population to show you how similar the results are. I m also going to show you data from the ongoing Phase IV study, I will show you data from the AERS database, and I will compare gemi s safety profile with that for antibiotics recently approved for an ABS indication.

Shown here are the most frequently occurring adverse events in gemifloxacin treated patients. The only adverse event occurring more frequently on gemifloxacin than comparators is rash, 3.5% versus 1.1%, and as Dr. Shear has explained, these rashes are generally mild to moderate, benign, and self-limiting.

Otherwise, gemifloxacin has a safety profile as good as that of comparators. The adverse events seen with gemifloxacin are generally mild to moderate in severity.

The next slide, this slide compares the overall clinical trial database with the five-day ABS sub-population, and you can see that the results are consistent, although there is a slightly lower rate with the five-day ABS sub-population. As you can see on this slide, when we look at serious adverse event rates, withdrawals due to adverse, and death rates, gemifloxacin s rates are at least as good as those seen with comparators. As for the seven serious adverse event rashes, Dr. Shear has already described the nature of those.

Here, you see the same serious adverse event data, withdrawals due to adverse events, and death rates comparing the entire gemifloxacin clinical trial database with the five-day ABS sub-population, and again, you see that the results are similar, although trending lower with the five days of therapy.

So to summarize, the safety data from these head-to-head studies show that although gemifloxacin has a greater rash rate than the

comparators, its overall side effects profile is at least as good as that seen with the comparators.

So we ve now reviewed the gemifloxacin results from the studies. I would now like to discuss the gemifloxacin side effects profile with the class effect of quinolones. First, gemifloxacin is not metabolized by any of the cytochrome P450 isozymes. It has no interaction with the system. It does not induce any of these enzymes. It does not inhibit any of these enzymes.

Gemifloxacin has a low phototoxicity potential comparable to that seen with ciprofloxcin. Gemifloxacin causes no significant glucose homeostasis dysfunction, as is true for some of the quinolones, such as gadifloxacin.

Next, I would like to move on to QTc effects. The clinical trials in patients have shown that gemifloxacin, on average, prolonged QTc by 2.6 milliseconds in clinical patients. I should point out that in the normal volunteers in the clinical pharmacology studies, among the 1,400 randomized to gemifloxacin compared to the 400

randomized to placebo, QTc prolongation was greater with placebo than with gemifloxacin.

No patients in the clinical trials were diagnosed with torsades. Finally, I should note that although it s always a concern with drugs that can prolong QTc interval as well as interact with the P450 system by inhibiting it or competing with it, gemifloxacin does not interact with this enzyme system and thus, this type of drug-drug interaction is not a concern with gemifloxacin.

Next, I d like to present the hepatic safety data with gemifloxacin. I will focus on alanine aminotransferase, since this is recognized as the most sensitive marker for hepatocellular injury. Shown on this slide is the incidence of ALT elevations in patients with normal ALT levels at baseline, and what you see is that the rate of elevation is low and that the rates of elevation are comparable between gemifloxacin treated patients and the patients treated with the comparators.

Importantly, no patients had ALT

elevations to greater than six times the upper limit of normal, no patients met Hy Zimmerman s rule for hepatic injury, no patients had concomitant ALT elevation with eosinophilia, which would indicate an immune-mediated hepatic dysfunction. Thus, we cannot find with these data any significant hepatic safety signal.

Next, I would like to discuss our Phase IV study. The FORCE study is a prospective randomized open-label study in patients with CAP and ABCB. This study was designed in collaboration with the FDA and is intended to reflect a real world setting where patients are either treated with gemifloxacin or commonly used antibiotics.

The study is intended to randomize 5,000 patients to gemifloxacin and 2,500 to active comparators. To date, over 5,200 patients have been enrolled in this study. In addition, 300 of the CAP patients are to undergo EKG monitoring at baseline and at the end of therapy to check for QTc effects.

Shown here are the most frequently

occurring adverse events on gemifloxacin and the pooled comparators, and as is true of the total clinical trial database, you can see that the rates of adverse events are at least as low as, or lower, with gemifloxacin compared to the comparators.

These adverse events are generally of mild to moderate severity, and as in the past, rashes generally the only adverse event occurring more frequently with gemifloxacin. So these results are entirely consistent with the overall clinical trial database.

In the FORCE study, if we look at serious adverse event reports, withdrawals due to adverse events, and deaths, what we see is that the rates are as low as, or lower, with gemifloxacin compared to the pooled comparators. Again, these results are entirely consistent with the larger clinical trial database.

The FORCE study data on QTc interval are shown here using both a Bazett s and a Fridericia's correction, and you can see that gemifloxacin did not significantly alter QTc interval. I should

also note that among all of the gemifloxacin treated patients EKGs, the maximum QTc ever seen using Bazett s correction was only 483 milliseconds, and using Fridericia s was only 464 milliseconds.

So we have now reviewed the clinical trial database of 8,119 patients treated with gemifloxacin, comparing it to the 5,248 comparators, and we have reviewed the 1,122 patients in the five-day ABS sub-population. These results have consistently shown a safety profile that is at least as good as that of comparators. With gemifloxacin, there is a greater rash rate. With comparators, there is a greater rate of adverse events involving other organ systems.

I would next like to turn to the post-marketing data, the AERS data. The FDA has looked at the crude reporting rates for gemi and other drugs, and for the other drugs, the period of review has ranged from two and a half to four years. This has resulted in up to a 20-fold difference in the sales volume.

I should note that although gemifloxacin was approved on the date shown, it was not launched until a year later, and thus, with gemifloxacin, we only have 1.7 years of data. I should point out, and in contrast to that, the other agents have been on the market for up to four years and thus, some of them are well past the maximal Weber effect; that is, the maximal reporting rate of spontaneous reports seen in the first two years following launch.

I should also mention that the FDA data does not show the overall serious adverse event reporting rates and the overall death reporting rates. Because of the Weber effect, we have chosen to analyze the post-marketing data using a cutoff of when approximately 350,000 sales were achieved. We chose that number, since that s where gemifloxacin is now. When you use these numbers, you see that gemifloxacin has an AE reporting rate that is greater than the other antibiotics, and this is due to non-serious rashes, which is not surprising in that rash is very apparent to the

patient, who can make it known to the doctor or the company, the FDA.

Rash is emphasized in both the physician s drug label and the patient information brochure, and in addition, these data are from both five and seven-day courses of gemifloxacin therapy, and as is mentioned in the briefing book and the labeling, rash is more common with seven days of therapy.

In contrast to the overall serious adverse event reporting rate, you will note that the cutaneous serious adverse event reporting rate is greater with gemifloxacin, but as Dr. Shear has indicated, these were not life-threatening rashes. More importantly, it should be noted that the overall serious adverse event reporting rate, the overall death reporting rates with gemifloxacin, are at least comparable to that seen with the other antibiotics.

Now, the AERS database is designed to help identify signals, safety signals, and it has identified a safety signal for benign rash with gemifloxacin. Dr. Shear has discussed in detail

the fact that these are not life-threatening rashes.

Because the AERS database relies in post-marketing -- that is, spontaneous passive reporting, another potentially more reliable source of data would be from the NDAs of antibiotics approved for an ABS indication.

Obviously, it s not ideal to compare data across NDAs. This type of analysis can introduce potential biases, just as using AERS data can. However, at least with this type data, we are confident in the numerator -- that is, the number of adverse events reports. We are confident in the denominator, the number of patients exposed. And we lack such confidence in the AERS database.

Shown here are the safety data taken from the summary basis of approvals of four antibiotics recently approved for an ABS indication. As you can see, although gemifloxacin may have a greater rate of benign rashes, the overall total adverse event rates, the serious adverse event rates, and the withdrawal due to adverse events rates with

gemifloxacin appear to be at least as good as that seen with the comparators.

With gemifloxacin, the adverse events are primarily related to the cutaneous system. With the other drugs, the adverse events are related to other organ systems.

So in summary, we have found that gemifloxacin has an acceptable safety profile, an overall safety profile, including adverse events, serious adverse events, withdrawals due to adverse events, that are at least as good as that seen with comparators.

Gemifloxacin adverse events affect primarily the skin. The comparators affect other organ systems. These results have been consistent across the total gemifloxacin clinical trial database, the five-day ABS sub-population, the ongoing Phase IV safety study, and the AERS database.

I would now like to turn the podium over to Dr. Patou to close.

DR. PATOU: Thank you, Dr. Waymack. I will

now summarize the main points of our presentation and describe our risk management program going forward.

It s important to understand that the paradigm for ABS treatment is changing. Physicians used to prescribe only the least active agents, holding the more active agents in reserve, but as Dr. Low has shown, less active antibiotics cause resistance. This can make entire classes of drugs ineffective in the face of serious diseases, such as pneumonia.

Thus, the changing paradigm supports the use of the most active agents in the class to benefit both the patient and public health. Today, many experts agree that patients who need antibiotic treatment for ABS need a drug that will cure their disease and minimize resistance.

Gemifloxacin does both. It has high in vitro activity against respiratory pathogens, favorable pharmacokinetics, activity against streptococcus pneumoniae, as well as multi-drug resistant streptococcus pneumoniae, and is the

floroquinolone least likely to cause resistance to streptococcus pneumoniae.

I d now like to address the controversy over the efficacy of antibiotics in ABS. As you heard from Dr. Ferguson, efficacy of gemifloxacin was shown in a large clinical program, which was conducted according to the published FDA guidelines for ABS trials.

These met all of their primary and secondary end points, and while there is discussion about the magnitude of the antibiotic treatment effect in ABS, there can be no doubt that gemifloxacin, with an 87 to 90% clinical cure rate, both in the overall, as well is in the large, bacteriologically evaluable population, is effective in ABS.

Additionally, gemifloxacin has been shown to be comparable to at least two other agents approved for this indication. We ve seen that gemifloxacin also meets the criteria of Drs. Sandy and Gwaltney s criteria for an ideal drug for ABS, and Dr. Low showed us that drugs that we consider

household names and standards of care in this condition fall well short of this ideal.

While there are approved drugs for ABS, only seven are considered really active, and only two of the seven are for short courses of therapy shown to be important in minimizing drug resistance, and one of these two drugs, Ketek, recently had a bolded warning on hepatic toxicity added to its label.

So clearly, physicians are losing choices in this indication. We need more drugs like gemifloxacin that meet the Sandy Gwaltney criteria. Now, we recognize that there is a signal for a higher rate of rash in the post-marketing surveillance reports. This is entirely consistent with the findings of the clinical trial program.

However, it is important to remember the following key points. We are asking for a five-day ABS indication. The rate of rash in our five-day trials was 2.5%, and as seen in the clinical trial program and confirmed by the post-marketing experience, the rash continues to be self-limiting

and clinically manageable, not life-threatening. It does not become SJS or TENS. There s a low cross- sensitization potential, and no subclinical sensitization.

In summary, the proportionately higher rate of rash with gemifloxacin does not equal a higher rate of potentially life-threatening cutaneous disease.

Now, I will turn to safety indicators other than rash in order to assess the overall safety profile of gemifloxacin. Gemifloxacin has demonstrated a favorable safety profile in multiple clinical trials of more than 8,000 patients and in the U.S. post-marketing database of 760,000 patients, both on its own merits and when compared to other drugs currently approved.

Perhaps of more importance are the lower rates of serious adverse effects, such as hepatic and cardiac events. We have seen no confirmed cases of torsades de pointes in the clinical trials and no glucose regulation problems. We ve also seen a very low rate of discontinuation and no

significant drug-drug interactions.

We fully recognize the morbidity associated with the reports of more severe cutaneous reactions, as there is with all serious adverse events reported with all drugs. However, gemifloxacin s safety should be judged based upon its overall safety.

As Dr. Waymack has shown, the overall safety of gemifloxacin is comparable to other antibiotics used in the treatment of ABS and respiratory infections. This has been demonstrated in the randomized clinical trials, in the post-marketing experience, and in the comparison to the SBAs, the summary basis approval, of other antibiotics.

Oscient is committed to ongoing safety monitoring and risk minimization for gemifloxacin. We have a proven track record of keeping our post-marketing promises and being vigilant in ensuring our programs are working. We minimize risk through our fixed-dose pack program, which we monitor through our Prescribing Use study. This

study, which was designed in conjunction with the FDA, monitors the prescribing patents to measure compliance with the intended duration of dosing.

We use a database provided by United Healthcare, an HMO of 13 million patients. With nearly 5,000 patients enrolled so far, we ve seen that the fixed-dose pack program is working. 92.8% of patients receive a single fixed-dose course of gemifloxacin, and only 3.1% of these courses were refilled.

We are committed to continuing this successful program. In addition, we plan to migrate our entire franchise to a five-day fixed course of therapy. The FDA is currently reviewing our five-day sNDA for CAP. We will continue our ongoing communication with physicians on the potential of rash with longer durations of therapy, and we will continue to publish results on drug safety, as we have for the last several years.

In conclusion, the data show a need for additional treatment choices in ABS. With an 87 to 90% clinical cure rate, gemifloxacin has

demonstrated efficacy and a favorable risk-benefit profile, confirmed in two years of post-marketing experience. Particularly today, with physicians seeking to tailor medications to individual patients, they need an additional ABS medication that meets published criteria. By every measure, gemifloxacin is that medication. Thank you.

DR. EDWARDS: Thank you. Thank you very much. I m sure all of us realize the amount of effort and time that has gone into this very clear and well-presented discussion. We are -- and I also thank you very much for being on time. We now have time for questions from the panel. Let me start with Dr. Poretz.

DR. PORETZ: I think it s clear that the drug has significant antibacterial activity and there s no question about that, but I have some questions about other rashes. I was surprised with the relatively low incidence of rashes secondary to betalactams in the comparator group; for example, augmentin, amoxicillin, clavulanate. I mean, the rash incidence seemed lower than I m used to seeing

in my type of practice.

One of my questions is also that many times, antibiotics are over-prescribed for viral infections, and with augmentin, for example, we ll see a disproportionate number of rashes, for example, in acute Epstein-Barr virus infection, and perhaps other viral infections.

Has your experience been that in viral processes or other entities, there s going to be greater incidence of rash, or is it mostly some hormonally-dependent process in women, whether they re taking birth control pills or estrogens that predisposes to the rash? Are there other variables?

DR. PATOU: So let me first, if I may, comment on the FORCE study and the observation of the perhaps lower-than-anticipated rate of rash in the co-amoxiclav comparator arm. That was -- that Phase IV study is an open-label study, so what we don t know is if physicians, knowing they re giving a drug where they have familiarity with the side effect profile, are modulating in some way their

reporting of their adverse events.

But certainly, I was involved in the development of augmentin, as well, and I would agree with you that we do tend to see a higher rate of rash. The rash rate described on the augmentin label is 3%, not so dissimilar to the overall rash rate we see with gemifloxacin.

We have looked at the effect of a number of parameters on the potential for the gemifloxacin rash, and what we did see was that there was some interaction with hormone replacement therapy in women over the age of 40.

But we were not able to directly -- we also did look, at one point, directly at whether the estrogen status of the patient did also affect the rash, and we looked at the points that patients were in different parts of their menstrual cycle in Study 344, and we could not discern any effect of estrogen level, except in that over-40 population with HRT.

DR. PORETZ: Birth control pills?

DR. PATOU: We did look at whether there

was an interaction with oral contraceptives, and we could not discern an association there. There was not an association.

DR. PORETZ: Could I ask one more question, Jack? You also had, like in any study, in the placebo group, a small percentage of rashes.

DR. PATOU: Right.

DR. PORETZ: Just for my own interest, were those placebo rashes biopsied, and what did they look like?

DR. PATOU: I ll ask Dr. Shear to comment on that.

DR. SHEAR: Yes, the study was blinded, so although rashes were biopsied, and the placebo rashes just showed the same sort of thing, a very mild perivascular infiltrate of a few lymphocytes, it was actually hard in this study because there were such little infiltrates. You d probably see more with a sunburn. I mean, it was just really hard to see much, and the placebo ones were very much the same as what we saw with the gemifloxacin rash.

DR. EDWARDS: Dr. Gross?

DR. GROSS: I m interested in the incidence of hospitalization in the gemi group versus the comparator group for those that had serious adverse events. I m also interested in the -- on Page 45, for the FORCE study, where we talk about gemifloxacin low rate of adverse events, the higher incidence of diarrhea, as we all know, C. dif is an incredibly huge problem these days.

Was there a higher incidence of C. dif in the comparators versus gemifloxacin, or was that not looked at?

DR. PATOU: Let me understand your questions correctly. The first comment you made was about the hospitalization in the cases of serious adverse events.

DR. GROSS: Correct.

DR. PATOU: I presume you re talking about in the post-marketing experience?

DR. GROSS: Well, let s take the FORCE study.

DR. PATOU: I --

DR. GROSS: Do you have any data on hospitalization --

DR. EDWARDS: Peter, can you push your speak button there?

FEMALE SPEAKER: Yes, because I didn t get any of that.

DR. GROSS: Yes. Do you have any data on hospitalization rates in the gemi versus comparator groups?

DR. PATOU: In the FORCE study?

DR. GROSS: In the FORCE study or any other large studies.

DR. PATOU: In the -- let me ask Dr. Waymack to comment on that. Excuse me.

DR. WAYMACK: We don t right now have serious broken down into hospitalizations versus medically significant or other ones. We can try to do that during the lunch break. It s just the serious, as is, is all of the death, life-threatening, requires prolonged hospitalization. We don t have anything further beyond that.

The question about diarrhea, in almost all of the studies, diarrhea was greater with the comparator drugs. As far as the C. difficile question, I first should preface by saying that in this medra (phonetic) world, whether -- if you put in C. difficile, you get C. difficile, colitis. If you put in pseudomembranous colitis, you get out C. difficile colitis.

In the entire clinical trial database, there is a single case of pseudomembranous colitis, which becomes C. difficile. In the post-marketing spontaneous reports database, there are 12 cases of C. difficile, half of which were reported as pseudomembranous colitis and then coded as C. difficile. The other half were reported as C. difficile, and that s -- the preferred term remains C. difficile.

DR. PATOU: We do have -- and we could bring up the precise data this afternoon, but in the post-marketing experience, we do have the duration of hospitalization for about half of the reported cases of hospitalization in the

post-marketing data. The majority of those were one to two days of hospitalization. In two cases, they were around eight days.

DR. EDWARDS: Yes, Dr. Bradley?

DR. BRADLEY: I had the opportunity to hear the presentation in March of 2003 with the increased incidence of rash in women under 40, and one of the questions then had to do with the mechanism and whether it was actually something related to estrogen, some sort of binding of the drug and then tissue binding in skin or something that correlates with estrogen.

I was just wondering if there s any work that you ve done on the underlying mechanism of rash in these women. Second question, of those who have rash, not in the clinical studies, but post-marketing, what percent of those actually feel a need to go back to their doctors and engender an additional medical visit because of the rash, and in the -- and how -- what percentage of those actually end up getting prescribed another medicine for the rash?

Because I noticed in the clinical trial reports, there were a number of patients that got dropped out of the gemi trials because they were prescribed steroids for the rash, which raises the question, how many of these people with rash will actually get steroids, which can represent another toxicity concern?

And then lastly, on Page 42 of your briefing document, the duration of illness in sinusitis with treatment versus placebo documents that there s actually no improvement in the clinical condition for the first five days of treatment. It seems to me that if there s no improvement in five days, the patients will certainly be wanting to go back to their doctors and get more antibiotic.

This is in contrast to your 3.1% of prescriptions being refilled in post-marketing, and that seems to be very, very low compared to what I would have expected based on your graph on Page 42.

DR. PATOU: You ve raised a number of points. The first -- maybe I could tackle your

last point first. I mean, I think I d like to say that in addition to looking at placebo controlled trials, I mean, there are other sources of evidence for a treatment effect of antibiotics in this disease, and I d also refer you to Page 41 and Table 18, where we look at different dose levels of antibiotics given in clinical trials, showing differences in effectiveness and whether the organism is susceptible or resistant, all of which we think provide good evidence for a treatment effect.

In terms of the likelihood that individuals receiving a five-day treatment of gemifloxacin for sinusitis, and then requiring a refill, we were able to look at this in our drug use study, because there were patients, even though the company -- and just to emphasize this -- does not promote the drug off-label, there are physicians who have used the drug in the setting of sinusitis, and were able to look at the refill rate in those individuals, and it isn t different from the patients with ABCB and CAP.

So I think we have a reassurance that of those treated, and there were a fair number of them, that actually, the refill patent is not likely to look very different.

In terms of mechanism of rash, we don t have any new data since 2003. What I think we can say is this is a remarkably well-studied rash. We understand all of the key variables here. But, in fact, we don t really have that mechanistic information for other common drug rashes, either.

DR. BRADLEY: And the rate of steroid prescription and doctor visits in patients with rash?

DR. PATOU: We would -- we have that information from the clinical trial database and we can go back and look at that and come to you with that. Actually, we have that information in Study 344. Slide on, please.

DR. BRADLEY: If I may.

DR. PATOU: Sorry, go ahead.

DR. BRADLEY: The clinical trial database actually wouldn t be as reflective of what goes on