in the real world, because everything is much more controlled. Everyone knows that anything that they give to the patient will be reviewed by the FDA and the company. I m more interested in -- I mean, this is reflective. I would expect, though, that this would be lower than what would happen in the real world.

DR. PATOU: Yes, we -- because of the porosity (phonetic) of information that we get on the post-marketing surveillance, it s really difficult to directly address your question in that particular setting.

DR. BRADLEY: Thank you.

DR. PATOU: Okay.

DR. EDWARDS: Rich, did you have a question?

DR. FROTHINGHAM: Yes. I wanted to first compliment you on your attention to post-marketing concerns, and especially this 344 study, which does indeed seem to be a landmark study.

As you know, the FDA, on prior occasions, concluded that the risks associated with

gemifloxacin outweighed the benefit for sinusitis. However, as you point out in your briefing book, prescribers continue to use this drugs for sinusitis, other less serious infections, and presumably, for non-bacterial infections, as well.

In fact, your prescriber use study indicates that pneumonia and bronchitis accounted for 39% of patients, sinusitis for 28%, and other indications for 33%.

Now, we recognize that off-label prescribing is very common, but in this specific case, the off-label prescribing for sinusitis was in the face of a prior FDA conclusion that the risk outweighed the benefit at that time, and I m wondering about any programs that you developed, as a manufacturer, to assure that providers were aware of that conclusion that the risk of this drug outweighed the benefit for sinusitis.

DR. PATOU: We make sure that in the training of our sales representatives, that they are very clear about what the drug is approved for, and that they should only be promoting the drug

based upon its approved indications, indeed (phonetic), the FDA, review all the marketing material that are provided by this sponsor and, in fact, all drug companies in that regard.

We are very diligent and careful to ensure that our sales reps stay within the label. I think that the patent that you re seeing is reflective of just what happens in terms of physicians making decisions themselves about how they should specifically sue a drug, but to be very clear, we ensure that we stay on label in our promotional activities with this agent.

DR. EDWARDS: Yes?

DR. BIGBY: I actually was present at the March 2003 meeting, as well, and reading the material, I was wondering what new is being presented to make the advisory committee change its mind. I think what I heard was an emphasis on five versus seven-day course of therapy and post-marketing surveillance.

Is that -- would you agree with that, or do you have other things that you would point out

as being newly presented that should make the committee change their mind?

DR. PATOU: Well, first, I d like to point out the committee has never opined on this indication. The indications brought in 2003 were only CAP and ABCB, so the prior discussion was that the FDA issued non-approval for the drug. This is the first time this committee has ever reviewed this.

We draw a number of sources, so you haven t reviewed the 7,775 patients of the original NDA, in terms of assessing this indication. But I would submit to you that we are bringing additional data. We re bringing over 1,200 additional patients, which are, in particular, in the disease that we re -- under discussion, ABS, we have 40% additional patients with a five-day exposure to gemifloxacin in ABS.

We also have our post-marketing data, which was an important post-marketing commitment that we were asked to deliver on by the FDA following some discussion, in fact, at the advisory

committee about continuing to monitor the drug in a Phase IV setting. And then importantly, we have our drug utilization study. We said at the time of the previous advisory committee that we thought that having only a fixed-dose pack of the drug in the marketplace would ensure compliance with the duration of therapy, and we established a program that we could actually monitor the effectiveness of that risk minimization, which I would submit to you is very unusual. Most sponsors aren t able to look at the effectiveness of their risk minimization program.

And then finally, we have the post-marketing experience, now almost two years of experience with the drug, the 760,000 exposures in the United States and another 200,000 outside the United States.

So we believe, number one, the committee has never looked at the sinusitis indication, and number two, we have really multiple sets of additional data that we re bringing to bear today, and they all show the same consistent finding, as I

mentioned earlier, the same finding throughout of a benign, self-limiting, exanthematous rash.

DR. EDWARDS: Okay. I actually have two questions for Dr. Shear. The -- I realize 344 has been reviewed previously, but in the information we have in the briefing booklet and the FDA booklet, I wonder if it -- I d like a little clarification on how those patients were selected for this study regarding their propensity to have a rash.

DR. SHEAR: Okay. So Study 344 was, in style, a Phase I study, using healthy volunteers. These are not people with infection. These are healthy volunteers in Phase I. And that s what the recruitment did show, they were sort of women between 18 and 40 who had volunteered for this study and were otherwise healthy. If you want to put the slide on, please.

They were people who had skin types one to four, which means it was white skin. They were using methods of contraception, and were otherwise healthy and negative for these other factors. So those are the people who are going into the study.

Is that what you re --

DR. EDWARDS: I believe you mentioned that they were likely to have a rash, likely to be more prone to have a rash.

DR. SHEAR: Oh, yes, right. The reason we say likely to have the rash is because -- if you want to go back to the actual presentation, and what we were trying to do there was enhance the rate of rash.

So we knew from the clinical trial data going in that when you cut the data, there appeared to be a higher rash rate in women under 40. So that s why it was women, and that s why -- now, actually, if you back up a bit. No, go to the next okay. Okay, put -- no, go forward. Forward, please. Yes, why don t you put that on, because I think that speaks to the issue, but doesn t answer the question, so I ll answer the question with the issue up there.

We talked about maximizing the rate of rash, so what we did was we knew with the clinical trial data going in that women under 40 had a

higher rash rate, because what we wanted was rash, because we needed rashes to study. You could do a study like this and wait forever to get a rash. We wanted rashes. We wanted to maximize the likely occurrence.

So women under 40 had a higher rash rate, so we said let s go for that. We knew that the rash rate depended very much on duration of therapy. That was the strongest factor. And so we gave the drug for 10 days, and so the drug was given for 10 days to women under 40 to try and maximize the occurrence of rash so that we would have rashes to see, to biopsy, and to analyze.

So that s what I mean by enriched. That was a specific population.

DR. EDWARDS: I see, but they didn t have any history of having had previous drug rashes --

DR. SHEAR: No.

DR. EDWARDS: -- or an allergic diathesis --

DR. SHEAR: No, absolutely not.

DR. EDWARDS: -- or anything like that? I

see.

DR. SHEAR: Yes, that s correct.

DR. EDWARDS: And then on a different subject, on the second patient with the possible Stevens-Johnson Syndrome, the one who was hospitalized for seven days, I m sure you ve probably given us all the information that s available on that patient there. Do we know anything about other drugs that might have been used concomitantly, or is there any other information regarding that case?

DR. SHEAR: Sure. Could you put that slide on? I can look at the report again later, but I pretty well wanted to summarize everything that was in here.

It was a very indirect report, so we really didn t have the physicians data. And for many, I have to say, though, reading all these MedWatch reports, it was really remarkable, the high quality a lot of the reports were, in terms of timing, so we could actually look at timing of onset, to look at -- and they specifically reported

negative findings. There was no hepatitis, there was no blistering, these types of things.

When we had medical reports, I have to say they are very high quality, and I thought it was a great success to be able to go through those, and it was a great opportunity. For this particular case, though, it was very indirect in trying to piece this all together, and I think what you have there is what you get, but I ll take another look.

DR. EDWARDS: Okay. Thank you. Let s see. I m getting behind. Yes?

DR. GUTIERREZ: Hi, I have a question for Dr. Shear, also. It s about 344 and I m just trying to understand this study in a little bit more detail. I notice on the algorithm, I think it s on Page 86, in the gemifloxacin group, of the individuals that had rash on gemifloxacin, it appears that there s a substantial number of individuals that did not go on to Part B of the study, and I was wondering if you could comment on that specific group of patients, and whether they, too, were biopsied, and whether their clinical

findings differed from the ones who did continue on.

DR. SHEAR: Okay. Can you put up that flow figure? No, the one that was in my talk. That has the numbers, but I just -- well, keep that one in hand, but go back to the flow one, because I think it gets confusing. Okay. Can you put that slide on, please? I don t have a pointer. Okay.

Without a pointer, which exact group are you talking about? We have -- so just -- I ll walk you through it, and then you tell me when I hit the hot spot.

DR. GUTIERREZ: Okay.

DR. SHEAR: The women under 40 were randomized to two groups at a 5:1 ratio.

DR. GUTIERREZ: That s correct, and in this manual here, it appears that in the gemifloxacin group, there were 260 individuals with rash.

DR. SHEAR: That s correct. So that would be this group here.

DR. GUTIERREZ: Right. And then they were further randomized to -- right now, I don t have my

glasses on --

DR. SHEAR: Cipro or placebo (phonetic).

DR. GUTIERREZ: It looks like 144, and then 51 with placebos, so that s 65 individuals, at least by my count, that appears to be missing from the part -- from the group that went to Part B. I could be wrong. I m just --

DR. SHEAR: Okay. You know what, then? Put up this slide that you have now. Okay. Well, you need -- if you don t have your glasses, you need binoculars for this one, but -- hence, my hesitation of putting it up. But what this does is try to explain the different groups.

DR. GUTIERREZ: That s great.

DR. SHEAR: So on the left, you have gemi, rash, Cipro. That s the group you re talking about?

DR. GUTIERREZ: That s the group I m talking about.

DR. SHEAR: Right, so the gemi rash Cipro group was 144 people. Gemi rash placebo was the next box to the right of that. That s over here,

and that s 51 people. And then -- so that s 195 patients -- I see what you re saying -- out of the 260, so people were not there.

DR. GUTIERREZ: Right, right.

DR. SHEAR: Yes, and we ll look at that, actually. I ll let Gary kind of comment.

DR. PATOU: We did look at that. We looked to see if there was a bias and if there was anything different in the severity of rash being reported, the nature of the rash, and we didn t see any difference in those individuals who withdrew from study from those who continued. So we don t believe that there s a sort of treatment bias here on the basis of those that withdrew from study. And people withdrew for a variety of reasons, I might add.

DR. GUTIERREZ: Okay.

DR. PATOU: Yes.

DR. GUTIERREZ: Thank you.

DR. PATOU: Okay.

DR. EDWARDS: Okay, Dr. Hilton?

DR. HILTON: Related to the same figure, I have

a question. So the overall rash rate in the gemi group for Part A was 31.7%, and if I compare that to the clinical trials data, it was only 15%. So I m thinking that for five-day data, also, 344 would ve given a higher estimate. So I m kind of concerned about that.

DR. SHEAR: Okay. Well, let s look at a few slides. Can you put on the slides of the pictures that I had, just to look at the rash? The photos. They were the three rashes. On a slide. Okay, next one. Yes. So can you put that on, please?

Just in terms of the reporting, I think that this type of rash -- and I can tell you, there are some red dots here, about the size of the point of the laser pointer here, scattered there, and a bit up on the shoulders -- for many of these rashes, patients don t report them or probably by the time they go to see the doctor, they re gone, because these are gone in a day or so.

And so I think that in real life, those occur, but just don t get picked up; for other drugs, too. I mean, it s something we do see. We see it

especially because we re-challenge patients sometimes in our clinic, and people do sometimes come back with a rash like this, say with ampicillin challenge, but that s usually in a day. They ll come back right away with something like this. This kind of thing is just hard to pick up, unless you have people coming in every day and are actually monitoring it.

On the five-day exposure, I mean, if -- well, just to reinforce this, if you want to put this slide up -- we did see the 2.6% rash rate, and your question is that if you went back and did a 344 type study in this group and gave everybody five days, what would the rash rate be; is that correct?

Well, I d have to think that you re going to pick up something higher than this. We do have different duration of therapy data, but I --

DR. HILTON: Yes, I m looking at your report, Table 36 on Page 75, so young women with 10 days exposure had 15% rash rate. So I m comparing the clinical trial data with the 344 data and seeing a doubling in those -- in --

DR. PATOU: I just want to make a couple additional points. The first one is, yes, the rash rate was 31.7 in that study. If you look at this slide, it s a little bit complicated, but if you look at females under 40, at 10 days, the rash rate here is 15.3%.

What you have to remember about Study 344 is that it was intended to elicit rash for study. So there is a potential for an ascertainment bias in the study. If, indeed, you look at the Cipro rash rate in the study and the reports of placebo rash, there s the suggestion that there is a sort of high sensitivity to reporting, since that was the issue under study.

What we believe is that this is the more real data, if you will, this is the actual descriptions by patients and physicians of what happened in the clinical trials, and that this is probably a better reflection of incidence, and that 344 is a very good study, but not a good study to answer an incidence question.

DR. HILTON: So also I think you re telling me

that the rash is self-limiting and therefore, not very serious and significant. But I m also thinking that ABS is somewhat self-limiting, because the table on Page -- the figure on Page 42 shows that the placebo subjects resolve about a week after the treated subjects resolve, so --

DR. PATOU: I mean, of course, there are -- I m going to ask Dr. Ferguson to comment. I mean, there are varying degrees of severity, and one of the issues in a placebo controlled trial setting is clearly how severe the patient population can be that you recruit to enable you to do such a study justifiably, but I ll ask Dr. Ferguson to comment on the burden of disease.

DR. FERGUSON: Slide on. This was a study done in Norway, comparing patients without sinus tap who had strong radiographic evidence of disease, and they were enrolled. What you see is that at Day 30, 25% of the patients with placebo were still sick. They still felt like they weren t improved at all. And less than 10% of the patients who had been treated with either amoxicillin or penicillin

reported that they were still sick.

But I d like to emphasize that placebo controlled trials, of which there are a half a dozen that have been reported since the Year 2000, have to be looked at very carefully, and there are no good placebo controlled trials in the literature.

Of note, in around 2002, 2003, Luxor (phonetic) reported that augmentin was the same as placebo for acute bacterial sinusitis, and that there was more diarrhea with augmentin, so you should not give an antibiotic for somebody with acute bacterial sinusitis. That was in their abstract, and that was in their conclusion.

And if you look through the materials and methods, it looked like it was a great study. The patients had to have radiographic evidence of the disease, they had to have nasal purulence and facial pain and pressure.

But if you read further into that placebo controlled trial, you see that they couldn t enroll enough patients in the first year. So they said,

well, you don t have to have facial pain and pressure and nasal purulence, you can have one or the other, because we still have the radiograph.

If you read further in that study, you find that one patient in the placebo arm had a brain abscess. If you look further back, when they re-reviewed their radiographs, 40% of them were normal. And so they said, well, we have this patient with a brain abscess. We can t have that. So if you have an elevated C-reactor (phonetic) protein, you can t come into the study.

So the whole study is one where you don t have patients who truly have bacterial sinus disease. And if you don t treat patients who truly have bacterial sinus disease, you can end up with a brain abscess.

DR. EDWARDS: Yes, Don?

DR. PORETZ: Just two quick things. You say that United Healthcare has followed 5,000 of the patients who ve been on gemifloxacin, as far as refill of prescriptions and so on?

DR. PATOU: Yes.

DR. PORETZ: Is that continuing? Do you plan on continuing --

DR. PATOU: Yes, absolutely.

DR. PORETZ: -- and that s a separate pool of patients who are going to be followed?

DR. PATOU: No, we will -- the beauty of that database is we will follow any individuals that subscribe to United Healthcare over the period of study. So that would include individuals that are already in the study, those clearly who enroll into that plan, and obviously, there ll be some that exit. It s a commitment that we ve made for a three-year period following the initial approval of the drug, and we re very happy to continue monitoring the effectiveness of our program.

DR. PORETZ: And just one more question, Jack.

DR. EDWARDS: Yes?

DR. PORETZ: Entirely different, about the C. difigan (phonetic). What is the anti-anaerobic activity of gemifloxacin, because there s a fair amount of questions about the more anti-anaerobic activities, some of the floroquinolones, the

greater the chance of potential C. dif, and as you market this drug over several years, you may see an increasing incidence of some of these findings.

DR. PATOU: Right. I ll hand over to Dr. Low to comment on that. Thanks.

DR. LOW: If I could have MB7, I think it is. And slide on. This is looking at repeated doses of gemifloxacin and the impact on the intestinal anaerobic microflora, and you can see that there is a response with regards to anthracocci (phonetic) and the streptococci, a miner response with E. coli, but a quick return to normal.

So yes, as you would expect with any antibiotic with a spectrum of activity, including gram negatives, that there would be an effect, but fortunately, it looks that the GI flora readily stabilized shortly thereafter.

DR. PORETZ: But, specifically for anaerobes, I mean, a recent article talked about a moxifloxacin having a high anti-anaerobic activity. How does this compare with other floroquinolones?

DR. LOW: The -- let me pull up the slide.

Slide on. This looks at the comparative activity of gemifloxacin, moxifloxacin, and levafloxacin against anaerobic organisms, and you can see that it s pretty well equivalent between the three members of the class.

DR. EDWARDS: Can we move on, Don?

DR. PATOU: There was a question earlier about the second possible case of SJS and concomitant medications. There s no drug information given on that form, no additional information.

DR. EDWARDS: Okay, thank you. Dr. Wong?

DR. WONG-BERINGER: I have two questions. The first one relates to Study 344. Do we know what proportion of those patients actually had prior floroquinolone history?

DR. PATOU: We -- they weren t patients, they were volunteers in the study, so prior usage of floroquinolones in Study 344, I think virtually none of them would ve received prior floroquinolones, yes.

DR. WONG-BERINGER: Okay. My second question relates to the time to onset of rash.

DR. PATOU: Sorry. I was going to say, though, we have that data from the clinical trial database, and prior exposure to a floroquinolone didn t seem to modulate the risk upwards or downwards for a gemifloxacin rash.

DR. WONG-BERINGER: How much of the patients were actually -- had prior history, in your clinical trial?

DR. PATOU: We should pull up the backup slide of prior quinolone use in the clinical trial database. Yes, that s -- this slide doesn t have the outcomes. We have -- it s a hundred and -- you know what? I m going to have to get back to you on that. We do have that data, yes.

DR. WONG-BERINGER: And my second question is -- relates to the time to onset of rash, comparing your post-marketing data versus those there in clinical trials. Is it possible to explain the earlier onset by patients who have been exposed to floroquinolones in the past, in the post-marketing data sets, perhaps a pre-sensitization?

DR. PATOU: We don t believe there is a

difference in the distribution of time to onset of rash in the post-marketing data. What you see is a bimodal distribution, and that bimodal distribution was seen in the clinical trial program.

From recollection, we had something of the order of 150 patients who had prior floroquinolones in the clinical trial database, and one or two of those developed a rash on gemifloxacin, so a similar rate to that seen in those who were floroquinolone naive.

DR. EDWARDS: At this point, we re scheduled for a break now, and we ll have time for additional questions later in the day. I d like to ask everyone to return at 10:30, when we ll begin with the FDA presentations. Thank you.

(Break was taken.)

DR. EDWARDS: We re going to resume the meeting now, and I m going to begin with Dr. Powers. John, are you ready? Okay.

DR. POWERS: Ready.

DR. EDWARDS: Okay. Could we have the -- we re now entering the phase of the meeting for the FDA

presentation, and I have elected to ask you all to hold questions until the end of the FDA presentations, unless there is a burning question that we could deal with expeditiously. Otherwise, we ll have an opportunity at the end for the other questions.

I m going to now introduce Dr. John Powers, who is a Medical Officer Team Leader of OAP, and he will be discussing drug development for acute bacterial sinusitis. John, thank you very much.

DR. POWERS: Thanks, Dr. Edwards. What we d like to address here in a very short period of time is issues in measuring effectiveness in trials of acute bacterial sinusitis. What we d like to go over are some regulatory and scientific issues related to non-inferiority trials in general, and how they can be used appropriately to demonstrate effectiveness.

Then we ll talk about the history of discussions regarding non-inferiority trials, specifically in the area of antimicrobials, and then even more specifically in acute bacterial

sinusitis trials, which we discussed with this committee in October of 2003.

Then we ll go through evaluation of the historical evidence of the magnitude of treatment effects of antimicrobials from an evaluation of placebo controlled trials in the trials specifically related to acute bacterial sinusitis, and then draw some conclusions regarding what our current status of knowledge is and how we evaluate effectiveness in ABS trials, and a little bit about in vitro resistance and how that affects outcomes.

Just a little bit of a -- expand a little bit on the regulatory background that Dr. Albrecht talked about, in 1938, there was only a requirement that FDA had to look at the safety of drugs, and it s interesting that that was based on deaths in children from an antibiotic, the elixir of sulfanilamide.

But in 1962, there was a requirement put in the law that drugs must demonstrate effectiveness, and the reason again was to balance any potential harms of therapy. Once again, that was based on a

drug that is used for an anti-infective indication, thalidomide, which now is used for leprosy.

But in those discussions in 1962, several interesting things came out. One was that President Kennedy sent recommendations to a Senate Committee saying that an undefined standard of what substantial evidence really is was inadequate in terms of assuring that drugs that reach the market have been shown to be effective for the claims made for them.

So what the President was really calling for was a very specific definition of substantial evidence, which is very different than the legal definition, which is more than a mere scintilla.

So he was calling for a specific definition, which Congress then defined that the only source of substantial evidence of effectiveness could be adequate and well-controlled trials; which then raises the question of what s an adequate and well-controlled trial?

So in 1970, FDA published regulations that provided criteria for defining what adequate and

well-controlled trials were, and they include these seven criteria, which are included in Section 314.126 of our current regulations.

The seven things are clear statement of the objectives of the trial; the study permits a valid quantitative comparison with a control, and the word quantitative is included in the regulations; that we select patients who have the disease, if it s a treatment trial, or who are at risk of the disease, if it s a prevention trial; that there s baseline comparability of patients so that any differences or similarities that we see are causally related to the drugs that were given, and not to some baseline differences; we should attempt to minimize bias by things like blinding; there should be appropriate methods of assessment of outcomes, and it says in the regulations that those outcomes should be well-defined and reliable; and finally, that we use appropriate methods of analysis.

Several court cases since 1970 have outlined that these are a minimal criteria for demonstrating

effectiveness. In 1985, however, there was an addition to the regulations because there was recognitions that there was issues with trials that attempt to show similarity of drugs that are not present in trials that attempt to show that one drug is superior to another.

Dr. Albrecht already read this to you, that this is still in our current regulations, that if the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between the treatments.

Similarity of a test drug and an active control can mean either that both drugs were effective, or that neither was effective. This refers to the setting of this particular trial. For instance, if we took antibacterials and studied them in people that only had viral infections, we would not expect to see a difference.

The regulations go on to say that the analysis of the study should explain why the drugs should be considered effective in that study; for example, by

reference to results in previous placebo-controlled studies of the active control drug. So this is making a link, then, between the current study that you re evaluating and data that comes from external to the trial from previous trials.

So what is a non-inferiority trial? A non-inferiority trial attempts to rule out how much inferior, how much worse, a new treatment might be compared to an already proven effective therapy, while at the same time ensuring that that control drug and the test drug s effect relative to a placebo is consistent in the conditions of the trial.

Another simple way to put this was, how would the test and the control drug stack up against a placebo group if a placebo group had been included in your current non-inferiority trial?

These issues were again addressed in more detail in 2000, when the International Conference on Harmonization Guidance E10 titled Choice of Control Groups and Related Issues in Clinical Trials described in Section 1.5 the information

that was necessary to select an appropriate non-inferiority margin.

They discussed that this is determined by an analysis of what s called the historical evidence of sensitivity to drug effects. Well, what does that mean? That historical evidence is the magnitude by which the control drug may be reliably and reproducibly shown to be superior to placebo from those previous superiority trials.

So again, this issue of magnitude gets to what it talks about, a quantitative comparison with a control drug which is part of adequate and well-controlled trials. The effect of the control drug relative to placebo should be well-characterized, and it should be consistent from trial to trial, so that the effect in the current trial of that particular control drug is consistent with what we ve seen in previous trials.

One can relate this to laboratory experiments. Well-designed experiments in the lab have both a positive and a negative control, and we use those to determine that the results that we re seeing are

causally related to the intervention, and not the conditions of the experiment. That s internal validity of the trial.

But in non-inferiority trials, there is a lack of a negative control group. There is no placebo group in a non-inferiority trial, in most of them, and that means they lack an intrinsic measure of internal validity.

So one of the issues that we talked about here is that the data on the effect of the control relative to the placebo is external to your current non-inferiority trial. That means that every non-inferiority trial has something in common with historical control trials.

At this committee, we have addressed several times in the past some of the biases that are inherent in historical control trials due to changes in medical practice, changes in the effect of the control drug, or changes in the design of the trial, in which case you re measuring the outcomes differently.

So one of the issues, then, that becomes

important in non-inferiority trials is not just selection of a margin; it s the conditions of the experiment.

For instance, enrolling patients that don t have the disease will make drugs appear more similar. Looking at a timing of an outcome that occurs beyond the natural history of when people would get better anyway will make drugs appear similar when, in fact, there may have been important differences that occurred earlier on and may change the effect of the control drug and change the conclusions regarding the margin chosen. So a margin that may have been appropriate at day three would not be appropriate at day 28.

So in end, what this means then is that demonstration of non-inferiority does not necessarily mean that the drug has demonstrated effectiveness relative to placebo in a current trial.

But the issue of selecting an appropriate margin is an important one that s integral to the design of non-inferiority trials, and what ICH E10

says about this is that in practice, the non-inferiority margin chosen usually will be smaller than that suggested by the smallest effect size of the active control, because an interest in ensuring that some clinically acceptable effect size, or fraction of the control effect, was maintained.

Now, that s not easy to grasp when you read through that quickly, like I just did. So what we mean by effect size here refers to the magnitude of the benefit of the active control drug relative to the placebo. Again, that information is garnered from previous placebo controlled trials, but we re assuming that that s going to remain constant in our current trial. We ll talk about what we mean by smallest effect, and I ll try to show some pictures of that.

So there then are three criteria that one needs to look at before you can perform a non-inferiority trial. One is that you need to do a quantitative assessment of the effect of the control drug relative to placebo based on data from

previous trials.

It s important to bring up this issue that we are not here today to debate whether antimicrobials in general are effective in the treatment of acute bacterial sinusitis, nor whether clinicians should choose to use them in practice. Those issues are one of practice of medicine. What we re here to talk about today is how do you study a new drug of unproven effectiveness in the setting of acute bacterial sinusitis?

So this issue of quantitation is very important. It s not just an issue of whether the drugs work or not. This quantitation needs to be reliable, well-characterized, and reproducible from trial to trial, and it must be based on trials that themselves are adequate and well-controlled. If not, we ve built the entire enterprise on sand.

We also should look at all previous superiority trials, not only those that show an effect, to get an idea of whether this is reproducible from trial to trial.

And then finally, we need to take into account

the variability in the data. In other words, we need to look at the error bars around these point estimates. I was taught in high school physics that every measurement has variability around it and some error, so we need to take that into account, as well.

After we ve done that and come up with a number that we re confident about, then we can select a margin that is less than the effect of the control relative to placebo in order to preserve some of the benefit of the control.

The whole idea of doing a non-inferiority trial is that the effect of the control drug is so important that we can t randomize people to placebo. Therefore, we don t want to select a margin that s equal to placebo, because we wouldn t be preserving any of the benefit of that drug.

Then finally, there s another issue, and that is that we need to make sure that the effect of the control drug is constant from trial to trial, and specifically, that it s constant in our current non-inferiority trial, and there are a number of

things that may change that assumption, and actually, that assumption is sometimes quite hard to verify.

For instance, there are some things that we can look at, and that is does the design of our current trial have similar definitions of disease, similar definitions of endpoints, and similar timing of the endpoints that are similar to those used in a previous trial that prove the magnitude and the effect of the control drug.

Those things, we can easily evaluate, but some of the others are a little more challenging, in terms of looking at changes in medical practice, changes in adjunctive therapies, and antimicrobial resistance, that may change the effect of the control drug. It s sort of an odd conundrum that we re saying we need new drugs because the older drugs aren t effective, and the sponsor showed twice a list of drugs that they thought are the only drugs left effective in sinusitis.

Well, if that s the case, then that really obviates doing a non-inferiority trial, if we re

saying that some of those other drugs are -- no longer have the constant effect that we think they had in the past.

So this slide, I apologize, is very confusing, and we had a lot of debate internally on this one. It s trying to define some of the terminology that s used in non-inferiority trials, and my subsequent slides will present this pictorially, so don t worry if the words don t make a whole lot of sense.

The first thing we need to look at is this thing called M1, and M1 is defined as that magnitude of the benefit of the active control compared to placebo. This is measured in our current trial, but it s determined from data in previous superiority trials. So this M1 comes from a determination of looking at all the previous placebo controlled trials and then hoping that that maintains a constant effect within our current trial.

M2 is defined as the loss of effect of the test drug compared to that active control, and

still considering that the drug is clinically meaningful. In other words, how much of the benefit of our control drug do we want to maintain?

One of the issues that comes up in non-inferiority trials is people often start by defining M2. They ll say, Well, I think it s okay that my new drug is 10% worse than the old drug. But if they haven t defined M1 first, that creates a problem.

So for instance, if we look at a drug that may be as much as 10% worse than the old drug, but the old drug was only 2% better than placebo, then our new drug may be as much as 8% worse than placebo; not that difficult math.

So what happens here is we only show effectiveness of the test drug when M2, that amount that we re going to allow the new drug to be worse, is less than the entire effect of the control drug relative to placebo, which is M1.

So all of those words can get quite confusing, so let me see if I can present this in a pictorial way. So let s take a disease where we know that

the benefit of antibiotics is quite large, like severe community acquired pneumonia.

We look at an analysis of previous data and we see that we think that antibiotics in general are as much as 25% better than placebo. But we need to, again, evaluate the error around that estimate as well, so we put confidence intervals around it and look at what the potential error of that is.

There s two reasons for doing that. One is there s error with this measurement, and the second one is that since we re not really sure that this same effect is going to occur in our current trial, we want to be suitably conservative, as it says in E10.

So that amount by which the drug is better than placebo -- and let me just say here that what we re looking at at the bottom axis here is not point estimates of effect, like the 87, 90% effect in sinusitis trials. We re looking at a difference between the control drug and placebo in this setting. So we re saying that for instance, this drug was 75% versus 50% for placebo.

So the M1 effect is the benefit of active control over placebo based on previous placebo controlled trials. But again, we don t want a new drug to be as much as 20% worse than the old one, because that will mean it will be equal to placebo.

So we want to preserve some of that benefit over placebo, so we select a number that is smaller than the total effect of the control drug which, in this case, is 20%. So our M2, then, is the acceptable loss of effect relative to control. Notice that this M1 is larger than the M2, which allows us to preserve some of that benefit. That s how we select a non-inferiority margin for a trial that we are then planning.

One of the other issues that comes up here, though, is we want to be sure of the reproducibility of the effect of that control drug, so we want to look at all of the previous trials and be able to see, as in this case, that we reproducibly show that large effect of the control drug relative to placebo.

So then what we do is we then move on to our

current trial, which is this bar in white, and again, we re talking about the test drug minus the effect of the control drug in this particular setting. So here, we ve got a test drug minus control drug that may be as much as about 8% worse than the control.

So what we see there is that allows us -- not only does it meet a margin of 10%, it allows us to preserve this much benefit over placebo. So it shows that this drug not only meets its non-inferiority margin, but also, preserves that benefit over placebo that we were worried about in the first place.

Now, what happens, though, if the previous historical data doesn t show a large effect of antibiotics relative to placebo? Well, then we re in a situation here where the effect of our test drug overlaps considerably with the effect of placebo, and there may be one trial that shows a large effect, but that s not reproducible from trial to trial.

So what do we need to do about that? What we

need to do about that is actually move the margin. So in this case, we couldn t justify a 10% margin; we would have to have a margin that, in this case, is essentially close to zero.

Well, a non-inferiority trial with a margin of zero is otherwise called a superiority trial, and what you need to do then with your new trial to exclude that there is a preserved benefit is you would need to actually show frank superiority of your test drug to your control drug, or to a placebo, in order to be able to preserve that effect.

So some people don t like looking at those treatment differences. It s very confusing. So this is one that s more in line with how the sponsor has presented the data in terms of point estimates of effect of drugs. So what you have in your current trial is you have drugs that say that the effect is in the mid 80% range, and you have some error bars around that, as well.

But you have to compare that to previous trials, so there are several assumptions we need to

make. One is that we have to assume that the effect of our control drug is constant relative to the effect that it had in the previous placebo controlled trials.

The other one is that we re saying that the effect of the control drug over placebo is quite large, such that when we do this control versus test here and we re relating it to a placebo group that is not included in our current trial, we are sure that this test excluded a benefit that is greater than placebo and preserved this much of a benefit of the control drug.

But what happens in the case where we go back and we look at the previous data and now, we re not so sure about the effect of the placebo? In that case, now, we see that both the control and the test overlap with placebo, not only in our previous trials, but in our current trials, as well.

So this is the situation that we have in acute bacterial sinusitis, where we re not so sure of the effect of control relative to placebo; therefore, demonstration that two drugs meet a chosen

non-inferiority margin may not be evidence of effectiveness of either drug in that particular setting.

Several meetings have addressed these issues in non-inferiority trials, specifically to antimicrobials. We ve had meetings in February of 2002, where we talked about this topic in general; July of 2002 on otitis; October of 2003 on sinusitis; and in all of those meetings, we discussed these issues related to acute exacerbations of chronic bronchitis. And then we had a workshop in April of 2004, again, where we talked about these issues, as well.

What came out of those was the need to evaluate data on each indication separately to determine the margins and whether the data do or do not support non-inferiority trials. We made a very strong case that there is no one universal margin for all different diseases. The issue with selection of patients with the disease has come up several times. We do need to select patients that have bacterial disease.

Also, the issue with defining outcomes and the timing of those outcomes is important, as well. Then finally, one of the issues we ve touched on is the differences in analyses between superiority trials and non-inferiority trials.

In superiority trials, it s well accepted that the intent to treat is the primary analysis. In non-inferiority trials, neither of these is optimal. The intent to treat makes drugs appear more similar, but the per-protocol analysis that is often used in these is a subgroup analyses, which may exclude patients post-randomization and eliminate the protection of randomization.

In October 2003, several of you were here when we discussed the clinical trial design in acute bacterial sinusitis, and what came out of this meeting was that no constellation of signs and symptoms predicts a bacterial etiology, so sinus punctures would be necessary in enrollment to define patients who actually have bacterial disease.

We also found no studies correlating that

greater than 10 days of symptoms show a higher rate of sinus puncture in people that would actually validate that criteria. It may be a great way to screen for people to tap, but it s not a substitute for taps.

We also talked about the lack of evidence of specificity of any particular radiographic findings with a positive culture on sinus puncture. So the radiographs, again, may help screen for people to tap, but are not a substitute for the tap.

We also talked about looking at previous trials that correlated clinical outcomes versus people that had a sinus puncture at baseline and an outcome, and we found no evidence to support the term presumed eradication that was in our draft guidance from 1998, because often, many patients get better, even when their sinus puncture is still positive at a test of cure tap.

So again, that becomes very problematic for us, to presume that the organism is gone, when we don t know that. We also talked that the timing of the outcome is important in relation to the ability

of the trial to evaluate effectiveness, and that time to resolution of symptoms may be the most sensitive measure of determining the benefit of antimicrobials.

And finally, that there was a lack of evidence from previous placebo controlled trials to base any non-inferiority margin, and that trials should be superiority trials to determine effectiveness.

So what we did, then, was we went back and we looked at the placebo controlled trials, and to do this, we used our own guidance for industry in evaluating clinical effectiveness of human drugs, and in there, in Section 3, there s criteria for evaluating published literature alone as evidence of effectiveness, which is what we are doing here. We re looking back at published literature to determine the effect size of antimicrobials in sinusitis.

So what this guidance says is we should look at multiple studies whose findings are consistent, they should have a high level of detail with prospectively determined analytical methods and

study endpoints.

The endpoints should be clearly appropriate and not dependent on investigator judgment, which many of these studies actually are, and that they should have robust results, not requiring post-hoc analyses or subsetting, like looking at only people that have positive cultures in an overall look at people.

So what you would need to justify a margin in acute bacterial sinusitis is a number of trials which show a large benefit relative to placebo. Some people have tried to pull these together in a meta-analysis, but that s very difficult in this setting because they don t meet this criteria.

These trials in sinusitis don t have a similar disease definition, they don t have similar endpoints. They use very different timings, which makes it difficult to assume the constancy of the effect of the control.

If you had something that looked like this, you could justify a 10% margin. What we have on the other hand, though, is trials that look like

this, where the magnitude of the treatment effect of control relative to placebo is unclear, which means that even a meta-analysis, then, would shrink this effect size and makes it very difficult to justify a margin of 10 or 15%, and in fact, means that we really can only justify a margin of zero, which is a superiority trial.

Just to briefly describe these trials, we evaluated 21 trials that compared antimicrobial to placebo in all languages. Four of them were not prospective, not randomized, or didn t look at direct patient outcomes. They looked at number of sinuses cured.

So that left us with 17 randomized prospective trials, which was a total of almost 3,000 patients, about 1,100 on placebo and about 1,300 on drug. It s interesting that even amongst the various drugs used, amoxicillin is used in five different ones at five different dosages and a bunch of different durations.

There were no quinolones tested in these, and one trial in children used cefuroxime. The reason

I mention that is that the sponsor s drugs are compared to trovafloxacin in one trial and in cefuroxime to the other.

These studies span 41 years, from 1964 to 2005, and of interest, eight of these have been published since 2000, two of them just last year in 2005, showing that placebo controlled trials can and are being performed.

In fact, when we look at the three that are performed, one was done in the U.S., showing that they can be done in the United States -- right down the street at Georgetown, actually -- one was performed in Europe, and one in the pediatric population. So even the recent studies show a mix of patients.

The average age for trial was 37 years and the average gender was about 60% female, which is important when we consider the adverse event profile of the drug that we re talking about today.

So here s what we saw in the 17 placebo controlled trials, and as you can see, 13 of the 17 have confidence intervals that cross zero, showing

no evidence of superiority of the drugs to placebo, and there s a number of drugs that are used over here, and the timing that s mentioned on the end of these is the timing of the evaluation, not the duration of the drug.

It s interesting, as Dr. Ferguson brought up, when you look at how these trials are done. For instance, the trial by Kaiser, when they looked at a subset of 77 people that had positive nasal cultures for strep pneuomo, H. floro, or moraxella, showed a benefit of antimicrobials, but a lower bound of the conference interval of 2.8%, which would not justify a 10 or 15% margin.

On the other hand, if you looked at all 265 people enrolled into the trial, the point estimate difference was zero, with 11% on either side. So how you define the disease is very important in these particular trials.

So again, what this doesn t allow us to do is to define a margin that s 10%, since many of these trials are to the right of that. So our review of this, then, shows no reliable, consistent magnitude

of benefit of antimicrobials compared to placebo; therefore, there was no evidence upon which to base any non-inferiority margin.

Again, this doesn t mean that antimicrobials are not effective in the treatment of sinusitis. We re talking about what it doesn t allow us to do is to pick a margin that would allow us to reliably study new drugs and ensure that they are better than placebo.

The majority of the trials do not provide evidence of benefit, but they are powered to rule out differences of 15 to 35%, which is what you would need to have a 10 or 15% margin. They are underpowered to rule out a difference of 1, 2, 5%. They are not underpowered to justify a margin of 10 to 15.

The trial with the largest point estimate of benefit had a 95% confidence interval lower bound of 11.3%. Even that trial would make it difficult to justify a 10% margin, because we d only be preserving 1.3% of the benefit, and most of the point estimates of treatment difference were

themselves less than 10%.

There is no way to just look at point estimates of success and make sense out of this, because the point estimates for success in the placebo groups range from 29 to 95%, so again, showing that a drug has 85, 87% efficacy by itself doesn t rule out that that s not near placebo, and the point estimates with the success for the various drugs ranged from 35 to 93%.

Again, several of these trials, eight of them, looked at long-term outcomes. There was no evidence of decreasing the complications or in prevention of chronic sinusitis. So since we can t pick a reliable M1, there s no way to select an M2 of how much loss of that effect we would want to be able to have.

Then finally, when we look at constancy of the effect of the control, we found that only two of these trials, by the same author, actually used consistent definitions for enrollment. I actually want to point that out, that the one trials that are actually done are the one by Lindbeck, which

the sponsor noted here, but the same group, Lindbeck, repeated that trial a few years later, in 1998, with a different definition.

In this trial, they used CT scans, which we haven t seen any recent trials use CT scans. In this trial, they evaluated people based on plain radiography, and again, they were not able to replicate those results.

So it s interesting to note, though, that when you look at the safety analyses for these drugs, that the majority of these, no surprise, actually show increased adverse events relative to placebo. So some of them provide the actual data, some of them didn t and just gave you odds ratios, so this tells us something we already know, that all drugs have adverse events, and we need to show that evidence of effectiveness in order to justify these adverse events.

The other issue that comes up here is what are the benefits of antimicrobials in sinusitis? They decrease facial pain, they decrease nasal congestion, they decrease -- they have symptomatic

benefits.

The interesting thing is that the qualitative adverse events here are of a similar nature to what we re trying to fix in sinusitis. So we may make somebody s nasal congestion go away, but we cause them to have diarrhea, nausea, abdominal pain, and other adverse events. This becomes an issue, too, when we talk about Clostridium difficile and its increasing incidence. That can be lethal. So we re talking about something maybe substituting a minor effect for a bad adverse event.

So then finally, to sort of stack this up, how do the sponsors three trials -- if we put them and stacked them up against the placebo controlled trials, does this justify a margin of 10%? Well, as the sponsor already pointed out, all three of their trials rule out a margin of 10%, but the real question is, is that proof of effectiveness? What we see is that these three trials overlap the placebo rate in a vast majority of these trials.

The other thing is this. This is an example of biocrete (phonetic), where we have a study drug

that was tested for seven days versus 10 days of an older drug, where we re not sure about the benefits, and then we proceed to test the seven days of our new drug against five days of a new drug.

So if we re not sure about the benefit of seven days, what does that say about comparing five to seven days, and so on down the line?

So just lastly, to comment on -- given our uncertainty about any magnitude of treatment effect with any drug, the correlation between in vitro resistance and clinical outcomes is also unclear. Even with susceptible organisms, there s a lack of a correlation between microbiological and clinical outcomes in this disease.

For instance, Carnfeldt, in 1975, stated Bacterial survival in the maxillary sinus, despite a high concentration, illustrates that MIC values determined in the lab do not always mirror the sensitivity of bacteria to antibiotics in vivo. Carnfeldt did another study in 1990 where they show that patients often recovered Clinically, despite

persistence of the organisms and differences in the potency of the antimicrobials.

They compared, in this case, cefixime to cefaclor, where cefixime s MICs were much lower than those with cefaclor; however, there was no difference in clinical outcomes, nor difference in bacteriological outcomes, in that study.

So in conclusion, then, there is a need for demonstration of the effectiveness of drugs relative to placebo in non-inferiority trials, and that s been noted since 1980 in the regulations. The evaluations of these previous placebo controlled trials in ABS does not show a reliable and reproducible magnitude of the effects of antimicrobials relative to placebo for studying new drugs in clinical trials.

Let me emphasize again, that is not saying that antimicrobials shouldn t be used in clinical practice, which is an entirely different question. The demonstration of non-inferiority in an acute bacterial sinusitis trial still leaves uncertain as to whether showing that you meet your margin

demonstrates effectiveness of the drug relative to placebo.

As we saw, even in the placebo controlled trials, demonstration of effectiveness is needed to balance any of those potential harms that the therapies might cause. Thanks.

DR. EDWARDS: Thank you very much, John. I d like to move on to the second presentation, and that will be by Maureen Tierney, who is a Medical Officer of DSPTP, and will do the medical officer review of the pre-marketing safety and efficacy data.

DR. TIERNEY: Good morning. I feel like this is dj vu for the members of the advisory committee who were here three years ago and Dr. Bigby from Boston. I did this three years ago, with obviously a different -- little bit of a different bent (phonetic), but I m happy to be back.

So what I m here today is to talk about the FDA s review of the safety and efficacy of gemifloxacin for acute bacterial sinusitis from the

clinical studies. What I ll talk about is -- and primarily spend time on the first two, which is the efficacy in acute bacterial sinusitis in the clinical study program and the cutaneous adverse events seen in those studies.

But to put that in perspective, we ll also talk about the cutaneous adverse events seen in the large database in NDA 21-158, spend a short time talking about QT and liver issues, and then finish off with an analysis of risk-benefit.

Now, many of my slides are going to show things that have actually already been shown to you, so when that happens, what I d like to do is just emphasize the points where there are differences in perspective or analysis from the company s presentation and from the FDA review.

As it has already been shown to you, the clinical program for ABS consisted of five studies. The first two, 009 and 010, were randomized double-blind studies of seven days of gemifloxacin versus comparators, cefuroxime and trovafloxacin, respectively. Only one of those studies, 009,

actually looked at clinical and bacteriologic result, and did do it using sinus puncture, which has been the most validated way for looking at bacteriology in acute bacterial sinusitis.

The five-day program consisted of three studies. 186 was the only randomized controlled double-blind study which compared five days of gemifloxacin with seven days of gemifloxacin. The two additional studies that were submitted were open-label, single-arm studies, both of which designed to look at bacteriology.

206 obtained the bacteriology via sinus puncture, but 333, which was the major addition to the data that we d already had on the clinical trials for ABS, was an open-label, single-arm study for which most of the bacteriology was designed for sinus endoscopy.

There were some isolets that were attained via sinus puncture in addition, but it was designed looking at bacteriology via sinus endoscopy, which has actually not been validated as a way to obtain bacteriology in ABS studies.

The inclusion criteria has already been discussed. Just the last two points, that because -- and Dr. Powers has alluded to this, as well -- because of the fact that the symptoms and also the x-ray findings don t have as high a correlation with disease, that it s really a recommendation from the advisory committee that sinus puncture really be required in all studies. Only two of the studies actually had sinus puncture required as an inclusion criteria for admission.

Now, the outcome criteria, in all these studies, the outcome, the primary outcome, was defined as the investigator determination of sustained improvement or resolution of signs and symptoms, such as no further antibiotic treatment was indicated, and it was at the follow-up date, which was primarily between days 18 to 24. It could range from day 16 to day 35, but primarily, was the day 18 to 24.

In some of the studies, we also have data at end of therapy and where that s pertinent, I ll refer to that. But bacteriologic success was

determined -- was really primarily presumed eradication. We ve also heard that that s something that we need to think about, in terms of future trials. But that bacteriologic success was defined as a clinical cure, and therefore, that was presumed eradication.

If -- you only actually required a sinus puncture is if you aren t feeling better. However, if you were feeling better and had a sinus puncture that showed that you d cleared your organisms, that would be a bacteriologic success.

Now, this is a slide which just shows you the five studies that were used for the ABS clinical program, and these are the -- this is the percent clinical success at follow-up. Most of my slides are actually going to present results related to an ITT analysis. Sometimes, I ll present both. Most of this applicant s slides have actually looked at a per-protocol analysis.

The per-protocol analysis, as I m sure you all know, differs from an ITT in the sense that ITT is basically all randomized patients who ve usually

received at least one dose of drug. A per-protocol analysis will include people who need to have completed usually about 80% of a drug and been present at the appropriate follow-up visits. There may be certain other issues, but those are the two prime differences.

But looking at these seven studies, we show that in the first three, which are -- these are your three randomized -- just see if I can get my pointer to work. Well, I can t get the pointer to work, so I ll just look at the first three clinical trials. Again, first two are seven-day studies. The third one is your five versus seven-day gemifloxacin study.

So the gemifloxacin studies are actually in darker green for your seven-day and lighter green for your five-day. Basically, the results, looking at an ITT analysis, show that the results are in the low to mid 80s for gemifloxacin and comparators. Same thing in the five-day to seven-day gemifloxacin. The results do go up in Studies 206 and 233, but I remind you that these

two are your open-label, single-agent trials.

I m just going to go back for a second, and just to also reiterate what Dr. Powers said, that in this study, which is comparing gemifloxacin to cefuroxime, cefuroxime had not previously been compared to placebo in adult acute bacterial sinusitis, but in a study in pediatrics, had not shown to have benefit over placebo. Study 010 compared gemifloxacin to trovafloxacin, which had never previously been compared to placebo.

This is a summary which just confirms the previous slide. It shows the confidence intervals of the treatment difference in the per-protocol analysis and the ITT analysis for the three randomized clinical trials, and basically confirms that in those trials, by the non-inferiority standards that were used for those trials at the time, that gemifloxacin did meet that non-inferiority standard.

Now, Study 186, I want to concentrate a little bit more on, because that is the only randomized clinical trial that we have for five days, and in

that trial, a little bit -- a little over 200 patients were randomized, and we have an ITT and a per-protocol analysis. That follow-up, again, which was about days 18 to 24, we show that we have a confidence interval that s within what was the non-inferiority margin that was set.

Also, for the ITT population, it s the same, and the results are very similar for five days of gemifloxacin versus seven days.

Now, when we look at the end of therapy, which is approximately days seven to nine, that same effect is not clearly preserved. In your per-protocol analysis, the results are quite high, at 93 and 96%, but when you look at your ITT analysis, it s 88.7% for gemifloxacin five days versus 95% for gemifloxacin seven days, and goes below a 10% non-inferiority standard.

But before I say that, in terms of using a term non-inferiority standard -- and one thing I d like to relate to what the company said earlier is clearly, our understanding of non-inferiority studies, and also, what s appropriate for ABS

studies, has been, in terms of the whole clinical and academic and regulatory world, been evolving over time. So the studies that were done for ABS and presented prior to 2005 met the standards of those studies.

But I think it s important, when we need to look at data, that we need to look at it in the context of all the information that we have available, and if we have evolved in our understanding of analyzing that data, need not to ignore any of that new knowledge, for example, that Dr. Powers has just presented in terms of understanding non-inferiority or some of the other issues related to understanding the effectiveness in acute bacterial sinusitis, such as looking at always trying to have sinus puncture data in a randomized clinical trial.

In addition, the advisory committee, I d recommend in looking at time to (phonetic) endpoints as opposed to follow-up endpoints.

Because another thing to point out with this slide, in terms of the difference that s seen at

end of therapy versus the previous slide, at follow-up, is that the further you go out, actually, usually, you are going to have less of an effect, and if the less of an effect that you have, the closer your two arms come together, the easier it is to show non-inferiority, but the harder it is to show superiority.

Just to mention a few things, microbiology has been extensively discussed by Dr. Low, and clearly shows that when you look at -- oh, I m sorry, this is the bacteriology FORCE Study 009, which, again, was the only randomized bacteriology study done, and it actually does show -- and this is the bacteriology ITT analysis -- shows that for all pathogens in an ITT analysis, about 85%, but this is eradication and presumed eradication, and versus 88% for cefuroxime.

Streptococcus pneumoniae, an 88%, but haemophilus influenza, slightly lower than 80%, with slightly higher responses in the cefuroxime arm. It was determined at the time that this study was presented that there was not enough data for

Klebsiella, staph aureus, or Moraxella catarrhalis to make a determination of true bacteriologic efficacy.

The data for Studies 206 and 233, because it has already been presented, and because it s open-label data, I m not going to further present it at this time, but just did want to mention our microbiologist had looked at the bacteriology of gemifloxacin way back for our 2003 advisory committee, and clearly, for all comers for your respiratory pathogens, the in vitro activity, so the MICs, for gemifloxacin are quite low, particularly for streptococcus pneumoniae.

But this does need to be looked at in relationship to the comparative PK data for quinolones, and the AUC and CMAX for gemifloxacin ranges lower than all the other quinolones, but particularly, about six times lower for moxifloxacin, which is the quinolone that has the most similar activity.

So just three points to remember, that the gemi MICs against quinolone resistant strep

pneumoniae are in the range of about .25 to 1 microgram per mil, whereas moxi s MICs are about four. For the strep pneumoniae double mutants, really, the range is similar. For gemi, about .25 to 1; moxi is actually about two to four.

It s here where we see the levo being very, very high. But again, put that in contrast to the gemi PK values being about six times lower than moxifloxacin.

So to summarize the efficacy, and particularly, some of the differences that we see, when you look at the seven-day, two non-inferiority double-blind randomized studies, we see a clinical outcome at follow-up of about 82% in the ITT populations to 90% in the per-protocol population, with a similar trend at the end of therapy.

The bacteriologic outcome in one study was about 85% for all pathogens, 88% for streptococcus pneumoniae, 79% for haemophilus influenza. But again, these were studies in a non-inferiority design where the comparators effect size had not previously been determined.

The five-day program includes one non-inferiority double-blind randomized study and two open-label non-comparators studies. The clinical outcome in Study 186, which is this study, at follow-up, was an ITT result in the ITT population of 83%. Again, the comparators effect size had not been determined. That was gemifloxacin seven days, which had been compared to comparators where the effect size hd not previously been determined.

Results were not completely consistent at the end of therapy and at follow-up, and for the five-day program, there is no randomized bacteriologic data that s been presented.

So basically, the overall I think summary or efficacy is has there really been an advantage shown for gemifloxacin in the treatment of acute bacterial sinusitis, and I think that s the point that we re trying to make, that we have not seen a clear advantage.

Now, we d like to move to some safety issues. First, I d like to look at the safety issues, the

cutaneous adverse events as they occurred in the acute bacterial sinusitis studies.

One of the reasons I truly want to focus on that -- and we will talk about the larger experience. Dr. Moshalder will talk about the post-marketing experience. But we re particularly concerned here in about what the cutaneous adverse event and other adverse event profile is in the demographics, the population that has a demographics of patients with acute bacterial sinusitis.

Now, Study 009, which was a seven-day study -- and the reason I am presenting the seven-day studies is because this is an ABS population -- in all the clinical trials for ABS that were presented, the majority of patients were women and the average age was usually between 38 and 40.

Here, in this seven-day study, there was a 10.6% incidence of total cutaneous adverse events. Now, I have presented the cutaneous -- the skin adverse events as cutaneous adverse events, which include rash plus urticaria, photosensitivity,

dermatitis. I did not include symptomatic issues, like pruritus, etc. But all of those are compared to the same type of events versus comparator.

Study 010, again, another randomized clinical trial, had a rash rate of about 10.9%. About half of those patients were determined to have a severe rash. Just to emphasize again, a severe rash is not the same as a serious rash. The serious rash has a clearly defined sort of regulatory definition. Severe is just on the spectrum of mild, moderate, and severe.

Now, when the data were looked at in the original submission of the seven-day studies, the trend that we ve all talked about is one of the first times this had been really evaluated, was determined that the rash rate in Study 009 was clearly higher for women under 40, but in Study 010, it was really significantly higher, at 17%. So 17% in the women under 40 who were in Study 010 developed a cutaneous adverse event.

It was really as a result of that finding, and the findings in some of the other populations of

the large database that was originally submitted, that it was decided that the risk-benefit did not support approval for seven days for ABS.

Clearly, as you ve all seen, when you go to five days for ABS, you significantly decrease your incidence of cutaneous adverse events. When looked in Study 186, which is our controlled double-blind trial, your total rash rate is about 2.8%, with only -- with actually no severe rashes in this setting. The comparators, we expected it to have a high rate of rash, because that was gemifloxacin seven days, which was close to 9%.

Study 206, which is an open-label trial that had over 450 patients, had 12 patients with cutaneous adverse events. 75% of those were women.

Study 333, another open-label study with close to 450 patients, had an incidence of rash of 5.1%, with two of those rashes being severe -- I m sorry, cutaneous adverse events, not just rash, because as we see, there s a -- four patients who have urticaria and two with photosensitivity reactions.

Now, when you compare your five-day

gemifloxacin data for ABS with your seven-day, and then with all comparators -- and this is probably the most important in terms of comparing the data for five-day, because it s focusing on five-day ABS -- but there, the total cutaneous adverse event rate is 3.1% in five days for gemifloxacin, 8.6% for seven days gemifloxacin, and 1% for all comparators.

To put in context our sort of understanding of the rash, I m going to review a little bit of the original NDAs, the population of 6,775 patients. Now, the total clinical trial database is 8,119 patients. The difference between the 675 (sic) is actually two community acquired pneumonia studies, one of which is open-label, and in patients with streptococcus pneumoniae, and in your ABS data.

Because these data had really not been looked at in quite the extensive way, when you look at the 8,119, as in the 6,775, I wanted to concentrate on just some of the information we can gleam from that. In NDA 21-158, we saw some trends, that there was a higher incidence of rash in the

gemifloxacin arms than all comparators; there was a higher number of serious adverse events and withdrawals than all comparators; the markedly high incidence in the enriched population of Study 344; and a higher incidence in any subgroup at any duration of therapy.

Just to recall, the patient population of 6,775 patients is folks for multiple different indications, so it included CAP, ABCB, complicated UTI, ABS, etc. The overall incidence was 3.6%. When you increase this number to 8,119 in the data that the company has presented, it was 3.5%, so there s not really much of a difference. There were no new serious adverse events in the 1,300 patients that were added here.

But also important to note, and haven t really been talked about quite that much this morning, is that we also see a pretty good incidence of urticaria in patients who receive gemifloxacin, and there was a .5% incidence of that actually in the overall population, and we saw more cases in the gemifloxacin arms in the five-day ABS, as well.

In asking questions about the severity of rash, in the overall -- this database population, 13.6% were reported to have a severe rash, versus 6.7% for all comparators.

This just confirms the -- what we ve all seen, is that there s a higher incidence in women as opposed to men. But one thing I d like to emphasize is it s actually a higher incidence in everybody under 40. There s a particularly higher incidence in women under 40, but men under 40, so in all comers. If we were to break this down to men under 40, women under 40, etc., there s a higher -- about a two-fold higher incidence in men under 40 than men over 40.

This just shows that when you increase age, that the decreasing incidence of rash continues really until the ninth decade, and that pattern is actually seen for overall and for women.

Lots of questions about onset of rash. This is a hard slide to see, but I calculated that if you look at overall -- the day of onset of rash, that if you look at day six -- now, if we re

talking about five days sort of duration of therapy, those folks rash will be seen on day six, seven, perhaps more, but a conservative estimate to look at, so close to 30% of the rash is actually occurring on day six or earlier, and that was in the overall population.

This just looks at the incidence in the ABS population in this large database, so this is all ABS, five and seven days, which gives you a combined incidence in that population of about 5.2% in comparison to 1% for comparators.

Now, Study 344, the nature of it has already been described, and the incidence of 31.7% in the gemifloxacin arm has already been talked about, so I m only going to talk about any differences in our presentation.

In this closely evaluated patient population, 7% of the rashes, or 19 of the total rashes out of 260 rashes, were considered severe, with none (phonetic) of the ciprofloxcin rashes considered severe. Okay.

This slide, I find one of the most sort of

telling things, in trying to determine how severe is this rash, how much is it going to affect folks, but in terms of the percentage of body surface area that s involved.

In this study, 25% of the women had a rash that involved over 60% of their body surface area. The characteristics of the rash, clearly mostly macular/papular, but 11% reported some plaques, and over 11% of women in this study had urticarial components to their rash, or urticaria just by itself.

In terms of another measure of extent of rash, we totally agree there was no SJS or TEN, etc. in this study, but 16% of the patients did report that they had some involvement either of their eyes or genitalia, just a small number, but that 12 patients out of 260 actually reported that they had some lesions in their mouth.

Now, obviously, that doesn t mean that you have SJS or TEN, but probably is some indicator of severity of rash.

Some questions were asked about treatment of

rash, and obviously, this is a clinical trial setting, but obviously, a lot of patients got antihistamines or topical steroids, but in terms of systemic steroids, we have the numbers that 12 out of 260 rashes in Study 344, so about 5% of the women in that study actually -- 5% of the rashes required treatment with systemic steroids.

In terms of the rashes in that combined clinical population of all comers for all indications, there were 241 rashes. About 27 of those actually required treatment with systemic steroids, and that s actually an incorrect number. That should be about 11%.

There were -- Dr. Shear presented some slides. You might actually recognize some of these pictures here. This is a slide of a woman in Study 344 who had onset of her rash on day eight, and her rash involved greater than 60% of the body surface area.

We do have great pictures of the rashes from this study, but none of the cases where there was reports of lesions in the mouth were there pictures of that mouth. This shows the rash in this

setting, and this shows the close-up of that rash.

This is another case of a woman really with a -- who had an onset a little bit earlier, on day six, who also had an extensive rash that required treatment with systemic steroids, and hers had an urticarial component, as well.

In terms of other safety-related issues or signals, when evaluating QTc potential, as we said, this is a quinolone; we need to think about and look for any issues of QT prolongation.

When one looks at QTc potential, looking at the inhibition of IC50 for inhibition of HERG channels, gemifloxacin is pretty much right in the middle of common quinolones, and we completely agree with the presentation that the clinical studies population had a 2.3 millisecond average increase, and that there are no unconfounded cases of torsades or significant QT population in the clinical population post-marketing.

The hepatic safety profile has often been looked at. In terms of -- just so it s understood, what are the preclinical hepatic findings for this

drug? Cholangitis, pericholangitis, with a patocellular degeneration and single-cell necrosis at high doses, also with crystalline deposits of the drug and biocanalicula, and then some elevated ALT and alk phos in the dog.

So it s just something we want to keep an eye on. We agree that it is not a major signal. In terms of the summary of our review of the clinical trial database, there was no patient who was in range at screening who bumped their LFTs to greater than eight times the upper limit of normal. There was one person who did go to eight times the upper limit of normal, but was elevated at beginning.

But one thing that we ve also kept in our mind is when you looked at the higher doses of gemifloxacin given for -- single doses given to women with complicated or uncomplicated UTI, four patients had bumps to greater than six times the upper limit of normal, and two, actually s, LFTs went up to eight times the upper limit of normal, and then came back down. So that s just one thing that we keep in mind and in close surveillance of

that.

In terms of the safety conclusions, there s a higher incidence of rash and urticaria, even at five days, which is a minimum of two and a half times to three times greater than comparators, depending on which set of data I think you look at.

There s a higher incidence of severe rash when you look at the overall population and withdrawals, low-grade liver and QT signals. And just one thing we also look at for the quinolones, there is no tendon signal at this time in the clinical trial database for quinolones, although I would like to mention that there was no tendon signals for any other quinolone in the clinical trial database, either.

So how do we look at the risk-benefit? Do the risks justify the benefit for gemifloxacin for five-day treatment of acute bacterial sinusitis? Now, this question really can t be completely answered until we -- or answered today as best it could be answered until we hear from Dr. Moshalder and the post-marketing -- his review of the

post-marketing data. But clearly, there s a higher incidence of mild to moderate rash, two and a half to three times.

I think the issue as to whether or not that s just inconsequential is, in a way, sometimes a matter of judgement, but there clearly is a higher incidence of mild to moderate rash. That has some morbidity. It might cause folks to be labeled as quinolone allergic and limit their -- the repertoire that s available to them in the future.

The question of sensitization we don t really feel has been adequately answered. One other thing I would like to mention, the company has presented a lot of the information on the FORCE data and the prescription use data, and has told us that those are interim reports. Because they re interim reports, we do not feel we can make conclusions that we can discuss publicly about those at this time.

But there really is not a lot of data on sensitization. In Study 344, there was a slightly higher incidence in the patients who received

ciprofloxcin after having a rash of gemifloxacin, 10% to 4%. But in terms of really a significant number of people who got gemifloxacin and then who got another quinolone or gemifloxacin again, there s really not enough data to make substantive conclusions.

There s a higher incidence of severe rash, although that incidence is lower in the five-day population. If indeed one has a severe rash, we ve seen in the general poop that about 10% of individuals who develop a rash will get treated with systemic steroids.

Also, I think the question of whether or not there s going to be an increased rate of serious rash, again, we should listen to Dr. Mosholder and see what he has to say. But the question of relationship of this rash and serious rash is a tough one, and the reason that s a tough one is if you actually look extensively at the literature, which I can tell you I did both in 2003 and this year, that it s very hard to say is there a correlation when one drug has a high incidence of

all kinds of rashes and then extension to SJS?

But one actually can say that of the drugs that have the highest association with SJS, and particularly, the sulfa drugs, of which are not approved for ABS, or at least one in particular, has the highest incidence of SJS.

So I think the question is can we say for sure there s going to be an increased incidence of serious rash? We don t know yes, we don t know no, but we re concerned about it. In terms of QT prolongation and liver, those are again signals low-grade that we need to keep an eye on.

So we do have some concerns about risk, predominately cutaneous adverse events, and I think at this point, we see that from a benefit standpoint, there s a small and questionable effects size, and no demonstrated advantage, and no demonstrated bacteriologic -- randomized bacteriologic benefit at five days at this point in time.

DR. EDWARDS: Thank you. Thank you very much. I d like to move right along now to Dr. Mosholder,

who s a Medical Officer in the Division of Drug Risk Evaluation, and he s going to review the post-marketing safety data. We re just a little behind, Dr. Mosholder.

DR. MOSHOLDER: Okay. Okay. Thank you, and my task will be to summarize the post-marketing surveillance data available on gemifloxacin. First, I ll be telling you about the extent of exposure in the population and some estimates of that, an overview of the AERS data, and some of this will recapitulate some of what you ve heard from Dr. Shear and Dr. Waymack.

I ll be talking about non-skin adverse events, cutaneous adverse events, and a special review of the serious cutaneous adverse events, and then finally, some concluding observations.

Looking at the extent of exposure of gemifloxacin in the population, as you ve heard already, it was approved in 2003, launched in 2004. One thing we ve found is that there s a large number of drug samples given to patients, so it makes estimations of the numbers of patients

exposed somewhat problematic.

The company s estimate, as you heard, 760,000 U.S. patients and about 200,000 outside the U.S. FDA s data vendor, Verispan, has two databases which we used for estimates. The total patient tracker counts the patients given prescriptions for the drug, and this estimate is somewhat lower, 330,000.

There s also a physician survey, which I can describe further if there s interest, but this survey would capture not only prescriptions, but also samples given to the patient by the physician, and this comes up with a higher number, about 1.2 million uses. Again, the sampling may account for the difference. So the ballpark estimate would be on the order of one million exposures, perhaps slightly less. So we want to look at the post-marketing surveillance data from the AERS database, and just -- this will be familiar to many of you, but we have a voluntary spontaneous reporting system that reports are collected through the MedWatch program.

It s particularly useful for detecting rare

but significant adverse drug reactions in the post-marketing population, and it has important limitations that all such systems have. Under reporting -- which I ll have some more comments on in the next slide -- there can be biases in reporting, as you heard illusion to the Weber effect, which says that newer drugs tend to produce more reporting by health care professionals.

Also, there s highly variable quality of information contained in the reports. The spontaneous reports are entered into our database, which is the Adverse Event Reporting System, or AERS database.

One thing we ll be talking about serious reports, and as people may be familiar, on the MedWatch form, serious cases are the ones where the reporter checks a box showing that they re fatal, life-threatening, involved a hospitalization, a disability, a congenital anomaly, or required some intervention to prevent permanent damage. There s also a box for other, where the reporter fills in the description.

So reports in which one of these boxes are checked are treated by the AERS database as serious, and I ll be coming back to that later.

Another word on under-reporting of adverse events, and as we go on to talk about so-called reporting rates observed in the database, it s important to know that those reporting rates are not incidence rates, because we would never assume that we have collected all of the reports that exist in the population using the drug.

There was a study in Canada -- and I should acknowledge, Dr. Shear actually is one of the co-authors of this study -- over a five-year period, 250 cases of TEN admitted to hospital burn units, but by cross-matching, it was found that only 25 of those were actually reported to the Canadian post-marketing surveillance system, or 10% of the known cases.

The authors went on to say that for less severe cases not requiring actual burn unit treatment, it was probably even a lower percentage. So that s just to make the point that especially in

general, and in particular, with cutaneous reactions, we usually assume we re seeing just a small fraction of the total cases.

So let s look at the AERS data for gemifloxacin as an overview, and this was as of last month. We had a total of 960 reports. About 9% of them involved one of the serious outcomes that I mentioned. The vast majority were from the U.S. There were only three from outside the U.S., and I ll say right now that all three involved a severe allergic reaction, two of them with cutaneous manifestations.

There was somewhat of a preponderance for female gender and older age group. By far, the leading system represented in these reports was the skin and subcutaneous disorders system, and I ll show that graphically here. Some 80% of gemifloxacin AERS reports from the U.S. are in the cutaneous classification. You see here some other antibiotics for comparison. You see for them, it s around 20%, in that neighborhood. So clearly, for this, gemifloxacin is somewhat unique.

So let s look at some of the non-cutaneous adverse event reporting data. Again, this is as of last month. We had approximately 180 reports that were not cutaneous in nature, 43 with a serious outcome and most of them in adults.

Looking at the serious outcome cases, where the indication was noted, it was sort of a distribution of bronchitis, sinusitis, which is, of course, off-label at the moment, and pneumonia. The most frequently reported serious adverse events were in the allergic category, and anaphylaxis and other severe allergic reactions, a total of 16, including both cutaneous and non-cutaneous.

We had Clostridium colitis cases and also perhaps an emerging signal of an interaction with warfarin, leading to increased INR.

We always want to look particularly at cases with a fatal outcome, and there are five summarized here on this slide. A 74-year-old male died with Clostridium colitis and toxic mega-colon one week after completing gemifloxacin treatment for bronchitis. There was a 47-year-old man who died

for unclear reasons -- there was no autopsy -- but he was known to have renal failure. A 33-year-old male -- this was previously mentioned in the company s presentation -- who died with hemophagocytic syndrome.

There was a death from cardiomyopathy, and a woman, a 66-year-old who reported hives and photosensitivity, and then some months later, died from complications unrelated during a surgical procedure.

So of the fatal outcome cases, we can say that the death from Clostridium colitis can be reasonably attributed to treatment of gemifloxacin. Looking at other events of interest, we ve heard about the cardiac effects and hepatic events, so we ll be looking at those. Clostridium, again.

There were 31 reports of the drug not being effective, 10 possible drug interaction reports, and perhaps an emerging signal for thrombocytopenia. There were three cases, two of which required inpatient treatment with platelet transfusion.

So going on to the cardiac events now, for QT prolongation, as we heard, there s some interest in that. There s really only one report. It was a sort of poorly described case of sudden respiratory collapse in a patient who had QT prolongation and was also hypokalemic, and this episode was never really explained. Could it have been an arrhythmia? It s very hard to say from the available information. There were also reports of tachycardia, but no malignant arrhythmias in that group.

For hepatic events, again, we ve heard about some findings with liver enzyme elevations. We have one case of liver failure, and that was the patient who had hemophagocytic syndrome. There was one report of colostatic liver injury complicated by concomitant simultaneous administration of another antibiotic, a case of hepatic steatosis, cholecystitis, and then some cases of elevated liver enzymes without additional complications.

So on balance, not a very strong signal for a serious liver injury in the post-marketing data

here. For Clostridium colitis, I already mentioned that we have some serious reports. There s an overall total of 10. We had the one death that I described and 40% of them had the diagnosis confirmed by culture or biopsy.

For drug interactions, of the 10 possible interactions, the majority involved warfarin, so that -- and some of those involved clinical bleeding episodes, so that could be an emerging drug interaction.

So that concludes my overview of the non-cutaneous reports, so we re going to focus now on the cutaneous adverse event data. As we ve heard already, the motivation for focusing on this is the strong signal from the clinical trials data. 32% of the patients in the special study 344 had a rash.

There were, again, as we ve heard, a total of seven rashes designated as serious by the clinical trial investigators out of roughly 8,100 patients exposed in clinical trials, so that s about one in 1,200 patients treated in the clinical trials had a

rash designated serious by the investigator.

So the purpose, as Dr. Tierney was saying, is to look to see if the spectrum of cutaneous toxicity in the post-marketing environment includes more malignant type rashes. So and actually, Dr. Shear will have reviewed some of these same data for you, and when we look to the end of May, there s a total of 799 reports. That s a crude count which may include some duplicates.

As I said, over 80% involved a cutaneous event and most of those were in females, and 6% of them were serious.

I won t go through the math in here in the interest of time, but the point here being that as was seen in the clinical trials, age under 40 years tended to be over-represented among the cutaneous event reports in the post-marketing data, as with the clinical trials.

In terms of time to onset, we took a sample of convenience, 291 cases coded with the simple medraterm (phonetic) rash, and the median time to onset here was four days.

Dr. Shear presented, actually, a much more detailed analysis of this, which tended to show actually kind of a bimodal distribution, and probably the median there would be around four days, as we saw. Speculatively, it would be interesting to know if the earlier onset rashes -- if those patients had had exposure to floroquinolones in the past, but unfortunately, I don t have that analysis.

For the serious outcome rash cases, this is just to say that many of the hospitalizations involved steroids, antihistamines, oxygen, and IV fluids. Hypersensitivity type events included urticaria, allergic vasculitis, and typical interventions would include epinephrine, steroids, and antihistamines, and some, but not all, had previous floroquinolone use or history of drug allergy.

Actually, you ve already seen this table presented, so I won t belabor it, but this is the crude reporting rates for serious skin events for th selected antibiotics. You see that, if you look

at these reporting rates, gemifloxacin sort of stands out.

So we decoded to do an in-depth analysis of the gemifloxacin serious events. For a comparator, we chose cefditoren, which has roughly the same level of use -- this is the estimate of prescriptions here -- and is also available only orally. So this is to talk about that in-depth review.

The cutoff date for that was August 2nd. There was special attention to cases that might represent the severe drug reactions that we ve been hearing about: SJS, TEN, allergy, and hypersensitivity.

Cases designated serious by the reporter -- in other words, that box was checked, but, which on review of the case itself, did not seem to warrant that classification, were excluded, as were cases in which the only skin event was really incidental to a different type of drug reaction, such as petikiae (phonetic).

So these are the results, and again, as we

heard earlier, we did not have any definite cases of Stevens-Johnson Syndrome. We had three possible cases, which Dr. Shear has already summarized in some detail. There was an additional fourth anonymous report, which I did not include here because it simply couldn t be verified.

For serious events of an allergic nature, there were nine, and then there were other serious events, most of these requiring inpatient hospital treatment, which did not appear to be allergic in nature. So for the grand total, 24 serious skin events, and then for the comparator drug with, under either estimate, a slightly higher level of use in the population, we have only three reports, and they re all in the allergic skin category.

I won t go into all this detail, but this is just -- and in the addendum to the briefing materials, there s a table summarizing all these cases. But just to illustrate, this was a 37-year-old male who completed a five-day course of treatment for sinusitis and bronchitis, developed a sore throat, rash, peri-orbital

swelling, fever, was hospitalized and treated with antihistamines, and then some other representative cases.

Then I wanted to draw your attention to this, which shows I think the limitations of the case information in many cases. Here, we simply notice a female in her 20s who, one day, after completing a five-day course for an unspecified respiratory tract infection, was hospitalized for rash. Treatment, further description, outcome all unknown. So I think that illustrates the limitations of what we re gathering from the post-marketing data.

This is to look at reporting rates for the individually reviewed cases that I just summarized, ad you see, if you look at all serious skin reactions, gemifloxacin a higher rate than cefditoren. If you look just at allergic reactions, however, not too much difference, although, as I ll say, those comparisons always have to be treated very cautiously.

So some observations, in the post-marketing