

comparative clinical and bacteriologic study. This was a study that was initially set up as a comparative study but when our guidance came out the sponsor stopped the study and put all the patients in a non-comparative trial. So, this did not have too many patients enrolled in the study.

For this study when you look at the end of therapy treatment azithromycin had an 88 percent cure rate.

The basic data from the study because this was a small study when you look at the Strep. pneumo at the end of therapy treatment end point there were 86 percent of Strep. pneumo cured versus H. flu 82 percent and 7 out of 7 M. catarrhalis were cured.

So, this basically gives you an overview of how they approved the 5-day regimen for otitis media in children. Was, as you must have already found out from the presentation this morning that there is scarce PK data in pediatrics, but when you look at the comparison of exposure among azithromycin regimens, 5 day versus 3 day, basically the conclusion drawn from studies that were submitted to FDA is overall exposure associated with 3-day regimen is similar to the 5 day.

When you look at the 3-day regimen versus 1 day in adults all we can say is overall exposure associated with 3 day may be similar to 1 day, but we can't make any

more conclusions than that.

In pediatric patients when you look at the 5 day versus the 3 day you can see that the 3 day may be similar to the 5-day regimen, and we do not have data from 3 day versus 1 day regimens in pediatrics. That basically gives you an overall of what we have already approved.

I will now go to the pivotal studies and go over my slides rather quickly because the numbers don't change. So, I will discuss the 1014 study which was the 3-day study first and then discuss the two 1-day therapy study and touch a little bit on the supportive study.

Study 1014 as you know was a clinical only study which was a double-blind multicenter randomized study comparing 10 milligrams daily dose of azithromycin given for 3 days with a 10 day course of augmentin.

Three hundred and seventy-three patients were enrolled for 28 US sites. The age group for entry was 6 months to 12 years and the mean age was 3.5 years.

I forgot to mention in the 5-day approval the cutoff age point for entry was 2 years and above. So, in that 5-day study none of the children were less than 2 years of age because that was the entry criteria. I forgot to mention that.

When you look at the MITT population and look at

end points at end of therapy and test of cure, the success rates for azithromycin were 83 compared to 88 for the augmentin group and when you look at the test of cure with it which was on day 20 to 32 apparently the cure rates flipped and in the azithromycin group the outcome is better than what you see in the comparative group, and I wanted to bring this to your attention.

When you look at the outcomes broken by age I may sound like a broken record, but anybody who is less 2 years of age the outcome for azithromycin is 75 percent compared to 85 in the augmentin group and when you look at children more than 2 years of age the cure rates are a bit higher than what you find in kids less than 2 years of age.

When you look at the test of cure visit you see the same thing. Children who are less than 2 years of age had a lower cure rate than children who were more than 2 years of age.

The second study is a clinical only study, 0581 which is a double-blind, double-dummy, multicenter study comparing a single dose of azithromycin with a 10-day course of augmentin.

In this study 350 patients were enrolled from nine US sites. The age group for entry was 6 months to 12 years and the mean age was 2.7 years.

In this study, also, when you look at the end of therapy and the test of cure the success rate at the end of therapy for azithromycin was 87 percent compared to 88 in the augmentin. So, it was similar and both azithromycin and augmentin had similar performance as test of cure.

When you break the clinical outcomes by age groups, children who were less than 2 years of age had a lower success rate than children who were more than 2 years of age and that was at the end of therapy. This is at the test of cure visit, and you see a similar pattern.

Study 1015 was a single tap open level non-comparative study which had tympanocentesis performed at baseline and 248 patients were enrolled from 22 US and Latin American study sites. The age group for entry was similar to the previous two studies. The mean age in this study was 3.4 years.

When you look at the clinical outcome since this was a non-comparative study azithromycin success rate at end of therapy was 89 percent compared to cure rates at test of cure visit which was 85 percent.

When you break the clinical outcomes by age it is the same story. You see here patients who are less than 2 years of age had a lower outcome than patients who were more than 2 years of age, and this was at the end of

therapy. When you look at test of cure you see similar numbers.

This study had tympanocentesis done only at baseline and there were 42 H. flu, 10 M. catarrhalis and 76 Strep. pneumo isolated.

When you look at the end of therapy assessment the success rate which is cure plus improvement 71 percent of H. flu had cured clinical outcome, 100 percent for M. catarrhalis and 92 percent for Strep. pneumo.

When you look at the clinical outcome at the test of cure visit 64 percent of H. flu were cured, 100 percent of M. catarrhalis and 88 percent of Strep. pneumo.

The sponsor gave you a detailed presentation about the resistance, but I am just going to mention that 16 percent of Strep. pneumo isolates were resistant to azithromycin and the success rate at the end of therapy and test of cure was 10 out of 12 and 8 out of 12 respectively.

When you break these two most common organisms down by age, when you look at the outcome at the end of therapy for H. flu patients who were less than 2 years of age the success rate at end of therapy was 61 percent compared to 79 percent for children more than 2 years of age.

In the Strep. pneumo group it did not matter.

Kids less than 2 and more than 2 basically had the same outcome. When you look at the test of cure in H. flu patients 53 were cured who were less than 2 years of age, but 72 percent who were cured were more than 2 years of age and for Strep. pneumo the outcome was lower for kids who were less than 2 years of age than who were more than 2 years of age.

So, basically it follows the same pattern.

Study 95001 was what the sponsor calls a pivotal study and was submitted to the NDA as part of a supportive single-step study which was done in one center only which compared a single dose of 30 milligrams azithromycin to 3 days' therapy, 10 milligrams daily with IM ceftriaxone.

Clinical evaluations were made at end of therapy which was days 9 to 19 and follow-up on days 26 to 44. The mean age in that study was 2.5 years and it ranged from 0.3 to 6.5 years. So, this study enrolled younger patients.

When you look at the clinical outcome by baseline pathogen at end of therapy for the two common organisms, as you know the sponsor presented only two M. catarrhalis isolated in the study and both were in the 3-day group. I wanted to concentrate on H. flu and Strep. pneumo.

When you look at the end-of-therapy evaluation the success rate for 1-day therapy for H. flu is 89

compared to 93 percent for the 3 days and 100 percent for ceftriaxone.

When you look at Strep pneumo, 95 percent for 1-day therapy, 83 percent for 3 day and 100 percent for ceftriaxone.

So basically that sort of summarizes all the studies that were submitted for this particular approval for 1 day and 3 day AZ. Just to sort of summarize study R-058 was a single dose comparative study which was a clinical only study, The study 1040 was a 3-day study which was also comparative to augmentin and 1015 was a non-comparative single dose, and it sort of gives you an idea of the cure rates ranging from 75 to about 85 percent, and bacterial outcome which was in the pivotal study where you know the H. flu was like 44 patient who had isolated, 10 and about 76 Strep. pneumo the clinical outcome in those patients who had H. flu isolated at baseline at end of therapy was about 68 percent compared to like lower sixties. M. catarrhalis all 100 percent were cured and Strep. pneumo had a better outcome at end of therapy and at test of cure.

So, this basically summarizes all the efficacy data that was submitted by the sponsor and FDA had a chance to review the source data and verify all the outcomes.

Just to make the discussion more complete we did go and look at the literature and in your briefing package I had included articles by Degan and others where two double-tap studies were done and we particularly looked at this because both the studies used azithromycin. One study used 3-day azithromycin and the other study used 5-day azithromycin, and there were low bacteriological eradication rates for H. flu when tests were done on therapy.

As I mentioned there are limitations of evidence from these publications because FDA has really not had a chance to review the source data from these publications.

One other published study that I didn't put in your briefing package but I handed it out and it should be in your package was a study that was done by Doern and others in Antimicrobial Agents and Chemotherapy this year.

This study looked at all the clinical isolates of Strep. pneumo that were obtained from 1999 to 2000. There were about 1531. This was more like a surveillance study where it looked at all the isolates and susceptibility of Strep. pneumo to several antimicrobial agents, quinolones, cephalosporins, macrolides and there was a whole bunch of them. Since the topic of discussion is azithromycin today from the particular paper when you look at all the clinical

isolates of Strep. pneumo 25.7 percent of them were resistant to azithromycin, but when you only took those isolates that were pain resistant which were like 329 isolates 77.2 were resistant to azithromycin.

Moving on to safety, all I need to do is point out a couple of ADRs that are of particular interest to us. As of June 30, 2000 cutoff point 2590 patients in all Phase II to IV studies, this is regardless of indications that they were entered and had received azithromycin and the sponsor presented adverse reactions which were treatment related.

I am going to show you a different picture in which all adverse reactions for all the otitis media studies, the numbers are the same, the denominators. These are the studies that the sponsor presented, also, but they presented the treatment related or what an investigator thought was, the vomiting was due to the treatment. I am looking at all adverse events since vomiting is really subjective.

So, when you look at all the patients with any sort of adverse reaction reported and in vomiting with yellow bile it is the 1 day. The turquoise is the 3 day and the red is the 5 day and this was taken from the original NDA and the comparator. In this study the comparator was

ceftriaxone and augmentin.

When you look at this vomiting almost 10.5 percent of patients vomited on day 1 whereas 6 percent on day 2 and a little more than 3 percent on day 3.

When you look at this particular group of vomiting and break it down to the days where these children vomited about 37 of 52 of the patients who reported vomiting on a single dose vomited on day 1 whereas there is only about less than 1 percent vomited in the 3-day group and about half of the patients vomited who were receiving the 5 day and then of course it decreases as you go out with 3, 4 and 5.

This concludes my presentation. I did not really go into detail because we basically did not disagree with the sponsor's data, but I would like to make the following acknowledgements, Dr. John Alexander and Dr. Thomas Smith did the primary review with me and Dr. Makhene, Dr. Soreth, Goldberger, Dr. Gavrilovic, Dr. Ross, and the project manager, Jose Cintron and our statistician George Rochester and the team leader Daphne. Mr. Harold Silver is our microbiologist and Dr. Sheldon. Dr. Charles Bonapace is our biopharmacist and Dr. Pelsor the team leader for biopharmacy. Dr. Andrew Yu is our chemist and Dr. David Katague is team leader, our chemistry team leader.

All of them were good moral support for me and participated in putting this presentation together. Thank you very much.

DR. RELLER: Questions for Dr. Moledina?

Dr. Chesney?

DR. CHESNEY: I had two questions. The first one I just wanted to clarify. You said that the 5-day initial azithromycin studies in children were done only in children over 2 or over 5.

DR. MOLEDINA: Over 2.

DR. CHESNEY: Over 2, and my second question is we have no pharmacokinetic data at all for azithromycin in children?

DR. MOLEDINA: I think they have some data, but Dr. Bonapace can answer that question.

DR. BONAPACE: The data we have in children consists of 5-day and 3-day regimens. The 5-day regimen is 12 milligrams per kilo and sampled only on day 5. We, also, have a 10 milligrams per kilo for 3 days sample on day 3 and a 20 milligrams per kilo also sampled on day 3. So, we do not have any information from the 1-day regimen in pediatrics.

DR. CHESNEY: Were those all in children over 2 years of age?

DR. BONAPACE: Most of the children were over 2 years of age, and there may have been maybe one or more down around 1-1/2 years but most of the children are over the age of 2, yes.

DR. RELER: Other questions for Dr. Moledina?

Dr. Wald?

DR. WALD: So, does that mean that azithromycin is only approved for use in acute otitis media in children over 2? Is that the current indication?

DR. MOLEDINA: No, the current indication reads 6 months and over.

DR. WALD: But there was never any data evaluated on children?

DR. MOLEDINA: I think there was some data not for otitis media, for other indications that children less than 2 years of age were enrolled and I think when the labeling was done those things were part of the whole package, and I looked at it. I was trying to go through the history and went through the whole 5-day package to see because the label is very clear but you know children less than 2 years of age were not enrolled in this particular indication, but when you look at the indication, you know, it is approved for anybody over 6 months of age, and I was not able to track down the history because the medical

officer has left FDA. So, I was not able to find anything but maybe the sponsor can answer that.

DR. RELLER: Dr. Leggett, and Dr. Dunne, if you and your colleagues have any comments on the pharmacodynamics, what data are available, with azithromycin we would appreciate hearing that and Dr. Leggett?

DR. LEGGETT: Question for either you or the sponsors, what are the kinetic data on the single-dose azithro for non-gonococcal urethritis or STDs? Do we have that data?

DR. ALEXANDER: That information was not submitted as part of this NDA, and the dosing of that is, also, different as well.

DR. RELLER: Dr. Gorman?

DR. GORMAN: I would like to follow up on Dr. Wald's question. Have any of the data that has been generated for this presentation, is it a response to a written request under the FDAMA regulations and is this being used as an application for pediatric exclusivity?

DR. ALEXANDER; This is Dr. Alexander. I am actually the pediatric representative for our division, but no, this isn't involved because azithromycin is a pre-1997 antibiotic. So, it doesn't qualify for exclusivity.

DR. RELLER: Dr. Dunne, do you have any comments in response to the queries raised?

DR. DUNNE: We do have data as was discussed for PK in children at 60 milligrams per kilo total given over 3 days or over 5 days. That is the PK that we have in children.

There was a study that was submitted to the agency after the original application in otitis media that looked at children down to the age of 6 months. We don't have that data available on slides today, but that was submitted, and it was used to amend the label to get the age group down to 6 months of age.

DR. RELLER: Thank you.

We will next go to the open public hearing. First the ground rules for this segment. I would like the presenters to disclose their position and any financial involvements that would be pertinent to the data presented.

Secondly, those presenters at the open public hearing can receive questions from the Committee but cannot be queried by the FDA nor the sponsor directly.

The total time allotted, not necessarily to be taken, but allotted maximum is 1 hour. The first presentation is scheduled for 20 minutes by Dr. Ron Dagan who will be followed by Dr. Jacobs and by Dr. Wolfe.

We have had a request for flipping those presentations, and we will do that. I had ranked them by time, not by my listing. I apologize for that. Dr. Jacobs will be 15 minutes and will be first followed by Dr. Dagan and Dr. Wolfe, if he be present after Dr. Dagan's presentation.

Dr. Jacobs?

DR. JACOBS: Thank you, Mr. Chairman, Committee members, ladies and gentlemen. I am Michael Jacobs. I am a clinical microbiologist in the Department of Pathology, Case Western Reserve University in Cleveland and I am, also, Director of Clinical Microbiology at University Hospitals of Cleveland.

I would like to start as far as financial disclosure is concerned that I have received financial support from a large number of pharmaceutical companies, and I provided this listing to the Committee which is available for inspection.

I, also, wish to state that I am representing myself and no one else in my capacity as a scientist and a physician working on principles related to the treatment of otitis media and I have submitted full disclosure of my work related to otitis media in this as well.

What I am going to be looking at today are some

of the principles involved in how you study this disease. Many of these have been covered and one of the points that we have been made aware of is that resistance in *Pneumococcus* and many other organisms has increased remarkably over the last 10 years and you can see here that treatment choices were a lot simpler pre-1990 than they are now, and we now have up to one-third or more of our strains of penicillin non-susceptible and up to three-quarters of the penicillin non-susceptible ones are macrolide resistant as well.

As far as macrolide resistance is concerned you have heard about 40 million doses of azithromycin being given since that drug was approved a few years ago and you can see what this has done to macrolide resistance rates. They were less than 10 percent or around about 10 percent in 1996, and they are now rounding at 25 percent and this has paralleled the usage of macrolides.

Also, just to give you a flavor of what has happened to susceptibility, I managed to get hold of some of the strains from otitis media that Dr. Halley had studied and Dr. Marchant had studied and you can see here that out of 50 isolates of pneumococci up to 1985 that amoxicillin, cefuroxime, cefproxil were very susceptible as were the macrolides with almost 100 percent susceptibility

whereas the MICs have now gone up more than 100-fold for many of these drugs and you can see that now we only have between 50 and 90 percent of our strains resistant to this example of drugs.

If you look at Hemophilus we have seen the same issue. Again, I managed to get hold of 50 isolates. You can see there is no shortage of isolates from the current era and you can see again that we have lost a lot of activity, far more strands of beta-lactamase producing. So, we have lost a lot of activity of amoxicillin. Cefuoxine has gone down as well, ceftriaxone/azithromycin and azithromycin have never had much activity against Hemophilus and I will get into that later on as well.

Now, as far as acute otitis media studies in children are concerned I am a clinical microbiologist, not a clinician, but being a clinical microbiologist the role of antibacterials is to eradicate the cause of organisms from the site of infection and as clinicians, Dr. Dagan and many other clinicians who have been involved in this area tell me that that is their goal as well, and if we fail to do this irrespective of clinical response we really are not doing our patients a service.

Now, what are limitations and the problems with outpatient clinical studies and respiratory tract

infections? There is a high rate of spontaneous resolution in these diseases that makes it difficult to show clinical differences between agents. These are very different diseases to diseases such as bacteremia and meningitis as examples.

The second point is if there is such a high rate of spontaneous resolution you really need to do bacteriologic outcome studies and these are not often performed due to necessity for invasive procedures such as ear, sinus and lung taps to obtain specimens.

More studies are therefore designed to show equivalent clinical outcome between established and new agents or in other words they are not statistically powered to show differences between agents and therefore if there are inadequacies of agents studied they are often not apparent.

Now, again, you have seen this, and again, I have simplified this going only up to 2000 patients in the study. The Pollyanna phenomenon published by Dr. Marchant and his colleagues and you can see here that when you are doing bacteriologic diagnosis and outcome that unless you have two very good drugs you need very few patients.

When you are doing bacteriologic diagnosis with clinical outcome you need larger numbers of patients and

you need the largest number of patients when you are doing purely clinical studies and you can see here that even if you are testing placebo versus a very good drug you need over 500 patients in a clinical study to make this point.

Also, to make this point this database is done predominantly on children under the age of 2 years of age.

Now, let us look at azithromycin and acute otitis media. There are four studies using a common comparator that I could find. The study designs differed. Two of them were clinical diagnosis and outcome. One was bacteriologic diagnosis, clinical outcome. One was bacteriologic diagnosis and outcome.

Patients ages in these studies differed considerably, and there has been discussion on this this morning. The first three studies involved patients from 6 months to 15 years old. Means were 4 to 6 years, while the fourth study involved patients only up to 4 years of age and the mean was 16 months, 1.3 years.

Sample sizes required for these studies to be powered to show differences between agents were determined based on calculations published by Marchant and this is what I came up with.

This is a summary of these four studies. You can see the mean age and the age range is given here. The mean

age was not given in the study but was presumed to be similar to these two studies given here, and you can see the differences that I pointed out.

The number were variable. You can see there were fairly large numbers in these two studies. There are very small numbers in the study done here and 143 in this study.

Study designs were these two were purely clinical studies. This was bacteriologic diagnosis, clinical outcome. This was bacteriologic diagnosis and outcome.

P value for clinical outcome was statistically significant only for the study with the lower age group patients. Number of patients needed to show 60 versus 90 percent bacteriologic efficacy is 2000 patients in these two studies. So, you can see that these studies were way under powered to show any difference.

So, it is not surprising that these clinical outcomes were not different. In the bacteriologic diagnosis clinical outcome 800 patients were needed, but you can see the P value was starting to approach significance even with 92 patients, and on this study which was the one done requiring the least number of patients bacteriologic diagnosis and outcome, there was a statistically significant difference in clinical outcome at end of treatment and also in bacteriologic outcome during therapy,

and you can see here the 143 patients met the criteria and that at least 100 patients would be needed to show a bacteriologic difference, sorry, a clinical difference based on bacteriologic diagnosis and outcome, and you can see here that if you had placebo you would need even fewer patients and in fact you can see the study sizes of these two studies were hardly able to differentiate any drug from placebo.

Now, the next issue that I am going to address is how can we overcome some of these limitations because it is very difficult to do studies that are powered to show these differences and one of the best approaches that I have been made aware of is to use pharmacokinetic or pharmacodynamic parameters to predict efficacy, and these are parameters that are very familiar to us, pharmacokinetics, serum concentration profile, penetration to the site of infection.

Pharmacodynamics is a relatively new field. It takes the potency of the drug in which we tend to spend a lot of time and looks at the actual way the bugs and drug interact in vivo, whether this is concentration or time dependent and whether the drug has post-antibiotic effects and basically agents can be divided up into two groups, those that are time dependent where the time above MSC of

the drug in serum is predictable outcome and those that are concentration dependent where either area under the curve to MIC ratio based on area under the curve in serum or area under the curve to MIC ratio will peak to MIC ratio are predictive of outcome and some examples of this and most of this work is taken from the work of people working in this field like Dr. Craig who was Dr. Reller's predecessor on this Committee and you can see here that in animal model this is a mouse model with Strep. pneumo infection you can see that mortality was reduced to zero once the percent or the dosing interval exceeded 40 percent of the dosing interval in serum for penicillins and 50 percent for cephalosporins.

There is human data which correlates with this very well. These are most of the double tap otitis media studies looking at bacteriologic outcome and you can see very clearly that to get greater than 80 percent bacteriologic eradication as seen with time dependent agents when the concentration of the drug is present for greater than 40 percent of the dosing interval and you can see that this works over a large number of studies, a large number of investigators and also applies to penicillin non-susceptible pneumococci, and if you correlate this with Hemophilus with a spontaneous resolution rate of about 50

percent you can see many drugs have been shown to be no better than placebo and with pneumococcus one study has come up with values that are very close to placebo.

Now, I am, also, showing you this data which you have seen before. This is the chinchilla model of otitis media with Hemophilus, to make a few points about this.

Firstly, when you look at this study here this shows azithromycin being given for 5 days and probably about double the dose equivalent that would be given to humans, but for the low dose which is the 30-milligrams per kilogram per day and the high dose it is clearly way higher than any dosing regimen that has been tested in humans, but you can see that when you follow the natural history of this out that this is no therapy, 100 percent of cultures positive on day 0, 100 percent on day 5 and in the chinchilla you get spontaneous resolution between day 5 and day 10, again very similar to that in humans, about 63 percent.

When you look at the lower dose, but again this is relatively high compared to what we are using in children, you can see that again you can get no change at day 5 but you are getting a significant decrease between day 5 and day 10 which is higher than that of placebo, and as you increase the dose even further you are getting 50

percent eradication at day 5 and almost 80 percent eradication by day 10.

So, there are some differences in this model between what happens in humans as far as natural resolution is concerned and what happens in this model.

When you look at this kinetically again you see the same thing and one of the questions I have about this model is when you take the drug and mix it with the organism in the lab the test tube you get killing very readily, and you saw some examples of that by the sponsor that by day 3, certainly within 24 hours in most cases you get a 3 to 5 log kill with azithromycin in *Hemophilus*, yet we are seeing absolutely no effect for 3 days, and I have a lot of questions as to why that is happening and what the mechanism is, and I don't know the answer to that.

Now, let us look at some other animal models. This is data that has recently been published in *Antimicrobial Agents and Chemotherapy* by Muttman et al. This is looking at azithromycin lung and plasma levels.

One of the points made is that drug delivery is very different. This is done intracellularly by macrophages and polymorphonuclear lymphocytes and the tissue level are more important than serum levels, and you can see here that if tissue levels are indeed important then tissue levels

would be adequate to treat Hemophilus whereas serum levels would not be, but if you actually look at the experimental data that you get you don't find that is the case.

Looking clarithromycin you get exactly the same parameters. You can see here tissue levels would be even less or slightly more difficult to be able to be effective against Hemophilus and certainly serum levels would not be effective.

When you look at the experiments that these investigators did what they found in fact was that macrolide susceptible pneumococci with both azithromycin and clarithromycin indeed could be treated very effectively based on dosing comparable to that given in humans and they used a whole dosing range here and they got a very nice straight line relationship.

They tested other agents which followed this line which I have removed for clarity, but when they started looking at macrolide resistant pneumococci and Hemophilus they found they had to go to much higher doses than those comparable to given in humans, and the dosing limit for azithromycin and clarithromycin for human dosage is approximately 25 milligrams per kilogram per day. In this model you can see that therefore this model was very effective in treating macrolide-susceptible pneumococci but

failed to treatment macrolide-resistant pneumococci with efflux mechanism not shown on the slide because they were off scale up here with ribosomal methylase which has very much higher MICs and, also was not effective against *Hemophilus influenzae* showing that again as had been demonstrated with many other organisms and drugs that it is the serum concentration of drug that is driving this not tissue concentration.

So, my conclusion from the study was that dosing comparable to dosing in humans azithromycin and clarithromycin were able to reduce inocula by greater than 3 logs in the lungs for macrolide susceptible pneumococci but were not able to do this for *Hemophilus influenzae* or for macrolide non-susceptible pneumococci with either resistance mechanism.

Let us look at the kinetics of azithromycin. This is a conventional dose, 10 milligrams day 1, 5 milligrams day 2 to 5. Area under the curve is 3 milligram hours per liter formula to get a break point for area under the curve divided by 25 gives you a break point of .1. This is again fine for macrolide susceptible pneumococci, fine for *Moraxella catarrhalis* but with an MIC 90 of macrolide resistant pneumococci of 8 is not very good for efflux strains or even worse for ribosomal methylase strains and

also with an MIC 90 of 1 to 2 for Hemophilus is way above the break point for Hemophilus.

Let us look at what is out there as far as break points is concerned. Pharmacodynamic break points based on pharmacodynamic principles are given over here and these are the ones that have been shown to correlate in animal models and in human data to what actually happens in vivo and you can see for the Pneumococcus the break points that we currently have approved by the National Committee for Clinical Lab Standards are pretty close to the pharmacodynamic break points. However, you can see there are some examples of NCCLS break points for Hemophilus which are higher than that of the pharmacodynamic break points and sometimes in some instances by up to 60-fold and you can see the examples I have given here of clarithromycin, azithromycin, loracarbef and cefaclor and cefprozil. Those stand out as being way higher than the pneumococcal break points or the pharmacodynamic break points, and one of the points about break points is for organisms causing the same infection there is no medical or scientific reason for a break point being higher for one organism than another.

Now, let us look at what happens when you look at susceptibility of organisms at different break points and I

am going to go over this quickly in the interests of time, but you can see that when you look at pharmacodynamic break points you get a very different picture with those examples of the break points that I showed you before when you look at NCCLS break points, and you can see in some instances there is almost 100 percent difference.

Is *Hemophilus* susceptible to azithromycin?

According to the pharmacodynamic principles it is not but microbiologically it is regarded as susceptible.

What I have done to summarize this data just to bring out the highlights, these are the drugs where greater than or equal to 90 percent of recent US trends are susceptible at both break points, and you can see here that amoxicillin, amoxicillin/clavulanate and clindamycin actually came in at 89 percent, but I included it anyway are the only three drugs that I could find that fulfilled this 90 percent criterion.

When you look at *Hemophilus* drugs that do this by both NCCLS and pharmacodynamic break points are amoxicillin/clavulanate, cefdinir, cefixime and cefpodoxime. Those drugs that do this only by NCCLS parameters are cefuorxime, cefprozil which comes in slightly under 90 percent, loracarbef and azithromycin.

Now, let us look a little bit about the specifics

of this. As you have seen pneumococci are divided up into three groups, and I think NSC 90 study that was presented earlier by the sponsor showing an MIC 90 of 2 micrograms per ml for Strep. pneumo is not representative of what goes on in the US. That study included US and Canadian data and there the MIC 90 was 2. More studies in the US have MICs in the 8 to 64 range.

With Hemophilus MICs are in the .5 to 4 range, unimodal distribution. You do find occasional strains with Hemophilus with much higher MICs, but what we have learned about Hemophilus in the last few years is that the reason they are much higher baseline than they are for Strep. pneumo is that they naturally have an efflux pump, and you can inhibit this pump and bring MICs down to about .06 micrograms per ml.

Unfortunately the agents we have at the moment that do this are all highly toxic. So, what you find with the Hemophilus is that the MIC 90 is 2 micrograms per ml. That is pretty universally accepted.

With Strep. pneumo it is now 32 micrograms per ml. How does this compare to break points? Pharmacodynamic break point comes out on current dosage to .1 microgram per ml. When you look at pharmacodynamic data in some of these more recent animal models this comes out to a break point

of roughly .5 micrograms per ml, and if you look at the dosing where they used doses equivalent to four times current human dosage they can bring this break point up to 4 micrograms per ml which will now include Hemophilus.

So, you certainly can get Hemophilus to be susceptible to macrolides in vivo, but you have to increase the doses enormously.

So, in conclusion antibacterial choices for empiric use in acute otitis media most clinical studies are too small to show clinical differences between agents. Pharmacodynamic parameters correlate with bacteriologic and clinical outcome in animal models and in humans and can be used to select agents with maximum potential for bacterial eradication.

Currently available agents vary significantly in achieving these pharmacodynamic parameters necessary for eradication and few oral agents approved for pediatric use are active against 90 percent or more of current US strains of the three key otitis media pathogens at approved dosage regimens, and finally, bacteriologic outcome studies in children and animal studies have repeatedly validated these conclusions.

Thank you for your attention.

DR. RELLER: Questions for Dr. Jacobs from the

Committee members?

Dr. Patterson?

DR. PATTERSON: Thank you for your nice presentation. Dr. Dagan's study that you cited, is that the one where H. flu was the most common isolate which seems to be a little different than the epidemiology we have heard today and wasn't the statistically significant difference in the H. flu infection?

DR. JACOBS: That is correct. The major difference in outcome there was based on H. flu. Dr. Dagan can probably answer this question better than I can, but I think there were a couple of points there. One is the age group that that study was done in was very different from the other bacteriologic diagnosis studies you looked at and many people believe that under the age of 2 Hemophilus is probably more common, and you had a second question, the statistical significance. Because of the MIC distributions we had very few resistant pneumococci there. So, with pneumococci the difference did not reach statistical significance but with Hemophilus with a unimodal population we had enough and that did reach statistical significance.

DR. RELLER: Thank you, Dr. Jacobs.

Dr. Dagan?

DR. DAGAN: I thank the Committee for allowing me

to say several things about methodology. I just want to tell you I am not from the United States. I didn't not know that I had to bring with me a declaration of with whom I was contracted but I did send it to the Committee, and you have it on record, and I reconstructed this from my memory.

So, if I forgot something you have that in your files. I have been receiving grants and/or consulting with Abbott, Aventis, and Aventis-Pasteur, GSK, Wyeth, Lederle Vaccines and Lilly Antibiotics, Pfizer, BMS, Lilly Chemopharmaceuticals, Astrozenica(?) and Merck, Sharp and Dohme. I may have forgotten something, but at least I think it shows you that I have quite a wide spectrum of working with various companies.

I thought that first I should answer the question regarding H. flu because I think Michael Jacobs did not answer that correctly. I am sorry, Mike. The study that you have, it was published in PIBJ in 2000. It is a multicenter study including many centers in the United States. When you analyze the data from the States separately H. flu was more common than Pneumococcus.

So, either it is changing with time or it is time and age. In France by the way it is the same thing. We have more Hemophilus. It is not unique only for one study.

I thought that in presentations of FDA and other

places a lot of data we probably saw so far 220 or 240 sites and there are lots of outcomes and a lot of data and it is very easy to get confused, and I have been confused for many, many years, and I think I am less confused now after working very hard in the last 5 years on otitis, and I would like to actually change this talk into a second one and try to really show this point which is I think very important to understand when we read results of studies or when we design the studies. These studies might be healthier to your needs.

If you know from preliminary studies the characteristics of your drug you can actually start and design your studies to show whatever you want to show and I think you had a little bit already in the talks and discussion before. I want to highlight that more to make it a little bit more clear maybe.

Now, first there is much outcome to choose, and I am not going to again tell you too much about the Pollyanna. We all know now about the Pollyanna effect issue, but I just want to show that this, if you take this outcome and again I will show you data from our experience where you really see a big, big difference between placebo and the best drug and this is something that can be easily demonstrated and ask a lot of questions, and I want to show

you this is as you already know much more accurate because the next big sample size and here you almost can show almost everything, and each one I will show you actually how to play with it in order to get what you really need.

This is a study that we published years ago looking at the cefuorixime-axetil versus cefaclor pharmacokinetics susceptible to penicillin. There was no problem. The two drugs are very, very efficient and both are effective but cefaclor is really much closer to placebo now than to cefuroxime-axetil and with Hemophilus, also, cefaclor is very much close to placebo compared to the other drug. So, here you can show with relatively small numbers of children as you can see, you can show your point in a very highly statistical significance.

This is another study that was not sponsored by the industry, but it was important to look at trimetapolis(?) sulfa because it is still the cheapest drug and we wanted to see what happens if you have susceptible or resistant and here unlike beta-lactams you have most of the time either highly susceptible or highly resistant and so when we get to children with Pneumococcus or with Hemophilus that were susceptible we have 100 percent success rate and in this case when we give, when they were resistant we had placebo effect in terms of bacteriological

eradication very clearly showing that for true resistant both Hemophilus and Pneumococcus this drug is the same.

When we look at Hemophilus influenzae now and we look at amoxicillin, there are three studies looking at it and here are the results with double tympanocentesis and with beta-lactamase negative Hemophilus you can see that in these three studies although they don't get exactly similar results they are clearly superior than placebo while for all three studies the numbers are small but very clearly you get placebo effect, again showing that if you have a drug that is susceptible to beta-lactamase then beta-lactamase producing organisms may fit a placebo. Again, very clear results. It is very difficult to argue with those.

You remember the point 12 cutoff that Michael Jacobs presented from the theoretical model. This is a study that we did sponsored by Pfizer a few years ago and published a few years ago, and looking at the bacteriological eradication and actually the only organism that could have an MIC less than .12 was Pneumococcus that was susceptible to macrolide and again we have 100 percent success rate here while those who were not were quite highly resistant and all of them as I said in this case. In a second study that we did we had close results to that.

For Hemophilus the lowest MIC we could get is .5 and as you remember the MIC 50 is one. Ninety is two. So, basically what we got is a success rate in all MICs very close to placebo. So, the only one that it was really shown to be good for is Pneumococcus that is susceptible to macrolides.

So, I think that those examples that demonstrate how you can go with relatively small numbers and get something which is significant and bacteriological proof and to the best of my knowledge otitis media is an infectious disease and the approach should be as for other infectious diseases. Go to the bacteria and demonstrate the eradication by antibiotics.

Now, which end point to choose? You already heard today a lot of discussion and let me just go back to this classical study by Kaleida that we have already mentioned. Now, which end point to choose? You already heard today a lot of discussion and let me just go back to this classical study by Kaleida that was already mentioned before and here these are children over 2 because you didn't use placebo under 2, but what is shown very clearly that at end of treatment she still had very good results with amoxicillin compared to placebo and this is looking at clinical outcome.

However, 2 weeks after the treatment there was no difference at all between placebo and amoxi and at 6 weeks actually placebo was significantly better in term of effusion. This is something which may be strange. It has some biological plausibility and I don't have time to speculate on that. Maybe if there are questions later on, but the point is very clear that if you choose this placebo is superior to amoxicillin.

Now, the whole issue of test of cure, I was surprised to hear that in this very, very important country they call this 1-month test of cure because they have never proved that this is a test of cure. Actually we have enough proof that it is not a test of cure.

If we look, this is a study that was mentioned already by Colin Marchant. If we look, and this is not the only study but this is the most recent one with the highest numbers. One hundred and eight cases that had double tympanocentesis studies. They had first tap with a bug. Second tap bud was eradicated. Children after treatment recur clinically. We go for third tap and now we can compare to the original organism. What we found was that of the 108, 20 percent were no growth. So, they had some viral infection or something or some technical issues. In 56 percent it was a new infection. New infection means either

Hemophilus was replacing Pneumococcus or vice versa or another bug, but that Pneumococcus was a different Pneumococcus was proved by serotype or pulse field or Hemophilus proved by pulse field or beta lactamase.

So, basically what we called test of cure is test of relapse or recurrence or bacteriological relapse because in only one-quarter of what we see of clinical relapse it is actually something that comes back and again, as discussed by Colin Marchant before it could be actually that the bug was eradicated but not from the nasopharynx and so far nasopharyngeal eradication or dynamics is not part of what the FDA wants to get for licensure although that might be very important. It might be in the future tested for that, too.

Then we had the Pneumococcus that recurred as Pneumococcus. This is 38 cases, 58 percent, almost two-thirds. It was not the same Pneumococcus and Hemophilus when recurred was Hemophilus in 60 percent almost. It was not the same Hemophilus. So, even when the same bug was there it was not actually the same bug.

So, the test of cure is for me not a real test of cure and maybe that should not be used. Who are the patient's contacts? This is very important, not who are the patients. Who are the patient's contacts? If you really

look the patients get the bugs from the contacts. If they have bad contacts, they have bad bugs, and this is a classical study that is hopefully going to be very soon published by Robert Cohen from Paris. He took only this experience of 5 days with this 10-day regimen. You know there is a big issue whether to treat 5 days or 10 days and took kids that are at home not going to day care centers and kids that go to day care centers. Otherwise these kids were comparable, and what you see first this is at end of treatment there were much more failures in those kids compared to those who are at home, but if you look at the 5 versus 10 days here you see a significant difference. Here the difference is not significant.

So, if you have a drug that doesn't do very well but you have still to show 5 days go for this, never go for this one-tailed. So, this is a test of cure which I call a test of relapse, okay? Again, much more relapses in day care centers. We all know that, but we never use that to read the articles, which were the kids from. Not only this, here it shows clearly that these kids who go to day care center 5 days is not appropriate, while here, no difference.

So, for kids who stay at home, fine. I never saw that in an article saying that for kids who stay at home you can give 5 days in our study, but if they go to

day care center be careful.

Kids who went to day care centers carry much more resistant pneumococci. This was found in so many studies and this is again from that study by Cohen. Not even that, kids who stay at home they may have brothers who go to day care center. Does this make a difference? Definitely. Pneumococcus twice as much carry Pneumococcus if their brother or sister go to day care center so with Hemophilus and Moraxella and even more than twice as much with any bug and this is highly statistically significant.

So, again, you don't get otitis if you don't have the bug in the nasopharynx. So, the idea is take the kids who don't go to day care center and who have no brothers and sisters and almost everything will work.

Age effect, we have heard about, but I want to just bring you something from the literature, very good studies. Some of them were used for licensure. Amoxicillin by Kaleida less than 2 years of age, 12 percent failures with amoxicillin versus only 4 percent above 2 years of age.

Hoberman, amox/clav published I think it was even used for the licensure of this drug in the previous dose and again this is not to compare from one study to the other because there were different outcomes, but within the same study 49

percent unsatisfactory. Look how much you go down with older kids.

Penicillin in Sweden after 2 years almost nothing and cefprozil the same after 1 year almost no problem. So, again, if I have a drug that doesn't show too much of an effect I will take the older kids and make it smaller.

Now, effect of severity, we had that. This is the Kaleida study non-severe disease, placebo, Amoxicillin .5 percent with unsatisfactory results at the end of treatment versus 6 percent, still a difference but not very impressive. You need a huge sample size for that while here you have a very impressive difference.

Again, if I have a drug that doesn't work very well I will go to those type of kids and actually if I go to the clinics and get kids over 2, up to 12 years of age I don't know how many of the pediatricians here treated how many kids, of course. It is very difficult to find them, and if you find them they usually have a little bit of ear pain, a little bit of red ear and you go to the clinic and you need to recruit a lot of kids because you get money per kid. So, you take all this was very mild, and this is in my belief the answer to that question that was asked before about why do we have so many older kids while almost all of our patients are younger kids.

Effects for this factor on acute otitis media, and I want to take all this together. I start to understand now how I can make things according to what I have. I just want to again last time come to this curve again to remind you of one thing. The worse the drug is the better the clinical efficacy is compared to the bacteriological efficacy. So, if I get a very bad drug then it looks much better on clinical, but if the drug is 100 percent I can almost never get really better than 90 percent because of those viral infections.

So, for me the maximum predicted for clinical success in bacteriological cases is about 90 percent. Above that you may be lucky to get a little bit more.

So, now, if I take three drugs or three arms in a study and this will be my last three slides, placebo, antibiotic A that is very, very weak and antibiotic B that is very, very strong I can predict something like that. You know that placebo is about, and I take kids under 2 to start with because these are the kids where you really can do double tympanocentesis. It is not really surprising that when you go for double tympanocentesis you don't go to older kids. You go to younger kids because they have the pus and they need those things and the parents or children will never submit themselves to double tympanocentesis when

they have a little bit of pain in the ear with a little bit of fraydrum(?). So, when I take the younger kids I will have here 30 percent placebo, 50 percent efficacy in antibiotic A and we saw already this is somewhere in the middle not very good drug and 90 percent which is one of the top drugs.

We have calculated from Colin's studies that were done together with Colin Marchant and from our own studies that were published before that if you see a bacteriological failure on day 4 to 5 about 40 percent only of those will be clinical failures. The others will still slowly go on and make better at the end of treatment. So, by using this calculation you can see that just for those if you go for clinical results you get 76 percent for placebo, 84 for the antibiotic A and 90 or better for antibiotic B.

Remember this 16 percent or 15 percent is exactly what you find in all the real good studies looking at placebo versus drug and this is what you find in almost all the studies with weak drugs in terms of success rate. They have around 76 percent success rate overall in cases where you don't expect the drug to work very well. This is placebo effect. This is the best effect. So, the effects are not very big. As mentioned before you have 24 million

cases in the United Otitis. Ten percent is 2 million cases. So, it is a big effect in general, but not in a study. So, to show the effect here you need as we showed before thousands of cases.

Now, let us assume that we took only the culture positive but 50 percent culture negative as we heard before, this is not appropriate in a study usually but 30 percent this is what you usually find.

So, if you take the clinical cases you have to also assume that 30 percent will be culture negative. Culture negative in my experience are always doing better much faster than anybody else, no matter if you give antibiotics or not. So, they actually are not bacterial where you miss the bug most of the time. They are not bacterial, and so if you include those 30 you already get to over 80 percent here, over 85 percent here and here again you cannot improve anyhow. This is the maximum.

Now, remember this is all under 24 months. Now, if you take kids over 24 months and here i don't put 60 percent as you had before. I just put 30 percent above 2 and of those only one-third above 3. So, it is still younger than most of the studies that have been used by many drugs. I get here over 85 percent. You remember this age effect. Here I get already equivalence antibiotic A and

B, but if I really want to show equivalence also as Colin said with tap water then I take those that are totally clinical, just looking at effusion and symptoms, and we all know that effusion and symptoms is most of the time otitis media, but sometimes it is otitis media with effusion just with a viral infection. How can you make really, there is an overlap. The overlap in this case with excellent investigators they only make an overlap in about 20 percent, not more than that. In other places I would say not, but in the United States there are excellent investigators. So, only 10 to 20 percent and here you have equivalence of one in three.

Okay, so, you can already play with this. So, if I summarize this, and in addition to that you heard that I can even make it more influenced by all those cases, avoiding or including those cases that are difficult to treat according to which drug I have.

So, now let us say that I am now a director of a new pharmaceutical company and I have either that drug or this drug. Unfortunately most of the weaker drugs are, also, convenient. Most of the stronger drugs in PKPD are not. I always cite my grandmother who says that a drug must taste like a drug. Otherwise it is not a drug. I don't know or they are injected which is another thing that my

grandmother would like, injections, but the point is if I have a drug here and we often have a drug with true bacteriological activity, efficacy as predicted by the PKPD in animal models and others but convenient and well tolerated versus another drug and on the other hand a drug that has bacteriological efficacy which is good by PKPD, etc., but is less convenient and less well tolerated, and I will give you a table how to construct studies to show to sell this one or I am not saying sell in terms of money, sell the idea to whoever needs to approve it or sell that drug.

I call it hand tailored AOM drug studies and this is the weak and well tolerated and the strong and less well tolerated, and what are the characteristics? Study population of course. I will try to have much more of the above 24. I try to take the younger ones that have real problem in spontaneous eradication. DCC, try to avoid DCC children here. Try to take as many as I can here. By using older kids you, also, avoid DCC because 6, 7, 8, 9 year olds don't go to day care centers. Other siblings at home? Try to take single kids, you know, so go to clinics where you have high society type of people. Don't go to the inner cities. They are going to fail. Recurrent non-responsive, avoid those. Put them in the exclusion criteria

but actually here try to enrich your population because those are the kids that are difficult to respond. So, enrich them in this, avoid them here. Baseline clinical diagnosis, never go to bacteriological here. Here clinical, we have proven bacterial etiology and tympanocentesis. Otherwise if you go here for clinical then you miss a lot of these things I said before.

Outcomes, tolerability puts much emphasis here because this is a drug that is well tolerated, of course. Try not to talk too much about this because it is not well tolerated. Convenience, the same. Bacteriological efficacy, don't include in your end points. Don't include that. Make it fit your main outcome here, okay, and make clinical outcome, test of cure. It is wonderful. They all go, Colin, your graph shows going down in parallel. I don't think you are right. They converge. They don't go in parallel. They converge at the end. There is almost no difference after 1 month eventually between those who responded well or not and so by going to the end of treatment I can show that everything is like everything, but here I am going to see the maximum difference and for conclusion I will be based on equivalence of clinical outcome and superiority of tolerability, convenience and here will be based on bacteriological and clinical efficacy

in difficult-to-treat cases.

Unfortunately, I am not American. I don't deal much with the FDA but my impression as an outsider being foreign and as you know we don't understand a lot of things in the Middle East until you find the situation similar to us and then we think alike.

I think that this is the FDA approach most of the time. So, if I have many drugs that may not be responding to this very difficult criteria, furthermore if I do this, people that are going eventually to take those meta analysis stuff and put them on a slide are going to show my end points inferior to their end points and they are going to say that there are some limitations to it, but I used what I have. When there is some limitation in using what you have you choose, also, what you want to choose. So, the point is here if you use this you are going to have lower end points in your drug and they are going to compare less favorably with this. So, I think that now I give you enough tools to plan your studies according to what you have in hand and my conclusion is with most of the acute otitis media with clinical outcome as currently conducted are virtually guaranteed to show no significant differences between agents, dosing or duration of treatment.

Thank you.

DR. RELLER: Thank you, Dr. Dagan.

Questions from the Committee for Dr. Dagan?

DR. DAGAN: Maybe my English was not clear enough.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: As a statistician I just thought that was magnificent. We are always looking for where the sources of variability are. This is beautiful. Thank you very much.

DR. RELLER: Thank you, Dr. Dagan.

Is Dr. Sidney Wolfe present?

If not, we will assume that Public Citizen's will not be making a comment at this meeting.

Before closing for lunch there are no direct questions that are permissible. Comments from either FDA or from Pfizer are possible.

Does anyone wish to make an additional comment now?

Dr. Alexander?

DR. ALEXANDER: If I could I just wanted to address a couple of questions that were asked earlier. One of them is related to the Costa Rican site and Hemophilus influenzae B and what we found looking at the bacteriology from the microbiologist was that there were patients who were identified within the trial but only a very small

proportion that did have Hemophilus influenzae type B, so that in the three arms there were 5 of 14 patients who were treated with the 3 day who had Hemophilus influenzae type B at baseline. Only 1 of 10 who was treated with the single dose had Hemophilus influenzae type B and 2 out of 9 who were treated with ceftriaxone.

DR. RELLER: Thank you. It is twelve-fifteen. We are exactly according to our agenda. We will reconvene at one-fifteen for discussion of the questions and vote by the Advisory Committee members.

Thank you.

(Thereupon, at 12:15 p.m., a recess was taken until 1:15 p.m., the same day.)

## AFTERNOON SESSION

1:15 PM

DR. RELER: Before beginning our discussion and vote on the issue at hand Tom Perez has an addendum to the meeting statement.

MR. PEREZ: Good afternoon. I stated this morning that Dr. Steve Ebert, Dr. Ellen Wald and Dr. Mary Glode would be excluded from participating in the general matters discussion of clinical trials of acute otitis media. I would like to correct the record and state that in accordance with 18 USC 208(b)(3) general matters waivers have been granted to all participants requiring a waiver. Therefore, Drs. Ebert, Wald and Glode will be able to participate fully in this discussion.

Thank you.

DR. RELER: Voting today will be the eight sitting members of the Advisory Committee, in addition the consultants, both Drs. Glode and Gorman will be voting members for today's meeting.

Dr. Soreth?

DR. SORETH: Dr. Reller, I wanted to give the charge to the Committee for our product-specific questions for azithromycin in the treatment of otitis media.

The first question, do the data support the safety and efficacy of a single dose, 30 milligrams per

kilogram and/or of the 3-day regimen of azithromycin for the treatment of acute otitis media?

We would ask the Committee that in their discussion they comment on the influence and the significance of the following and how they contributed to the Committee's recommendations.

The interpretation of the data from clinical only studies, the interpretation of the data with regard to studies that have microbiology with the tympanocentesis at baseline on single tap, the natural history of the infection and also information from the published literature and how that influences any specific recommendation. Should the Committee recommend approval we ask further if there would be any caveats in the label based on the results of the studies with tympanocentesis at baseline. If the Committee does not recommend approval what additional study or studies and finally, if approval of the single-dose regimen is recommended we ask the Committee for their advice with regard to what we would advise prescribers and patients concerning increased vomiting associated with the use of the single-dose regimen.

DR. RELER: Thank you. Tom Perez will be recording our votes yes or no. Based on past experience in

the discussions I think it would be helpful if we heard from every Committee member the points of discussion that you wish to make regardless of in the end how your vote is recorded so that the importance of the various components that Dr. Soreth has asked us to comment on we now open it up for discussion.

Dr. Chesney?

DR. CHESNEY: I have a real concern about our lack of pharmacokinetic data. In terms of giving this drug only once or for 3 days I don't know No. 1 if it is taken up into hepatocytes. No. 2, I don't know how very young infants will handle this and No. 3, one of my concerns is that children with viral syndromes not infrequently have elevated liver function tests, and I am not sure if these high doses are taken up into hepatocytes how that could influence the course of the viral syndrome particularly since it may be retained for a prolonged half life.

So, I am very anxious about not having pharmacokinetic data particularly in younger children and I don't know if anybody can reassure me on that score.

DR. RELLER: Other comments from the Committee?

DR. LEGGETT: Jim Leggett. Several thoughts occur to me on a purely scientific basis. PKPD has not been shown to work either for the single day or the 3 day. There is

some data with the single dose in other uses leading to increased harboring of resistant organisms. That worries me a little, and in terms of AUC to MIC while that may be the parameter of most importance for azithro, that is, also, a little bit experimentally biased by the way and the timing that those parameters are done in mice and everyone else, and I worry a little bit about a single dose study finally running out of its post-antibiotic effects before we get out to the longer time period at least in terms of having efficacious levels, especially in view of the 5-day versus 10-day French data of Dr.Cohen that was presented.

So, in other words if 10 days is better in these sickest patients than 5 days then what does the single dose really do for us in terms of actually treating the patients?

I don't know anything about regulations in terms of whether we should approve the 1 day or the 3 day because a lot of the steps that are in the guidance document appear to have been addressed.

However, I am very much worried about the lack of pharmacokinetics in both the 1 day and the little less than 3 day.

I think that in terms of interpretation of data from clinical only I think that end is where we are

beginning to see, at least possibly see today leads to sort of a bio-creep that people are worried about so that we keep comparing ourselves to less and less and less and finally we get down to no better than placebo.

I am, also, a little bit worried about the clinical only, of the difficulty at least I as a non-pediatrician have in making the difference between cured, improved and failed on looking at an ear or in an infant. I think tympanocentesis at baseline to me is a step better. The natural history of the infection looking at the degree of recurrences means that waiting until the test of cure does not seem like a very good idea, and information from the published literature I think of good quality is very useful in terms of placing these things in perspective if we only have active control comparators. It gives us a little bit of an external grounding at least to some degree.

In additional studies I would recommend further kinetic studies. Vomiting with a single dose, I think it has to be stated. I am a little bit worried again with kinetics that those values, the AUCs that were shown in adults for the single dose 2 grams and 3 grams while the yellow and green triangles were within the error margin the AUC in those things said, "Only 0 to 24." With a half life

of 68 hours we are still accumulating. I don't know what is going to happen, again to go back to my point, they vomited, it looks fine up to 24 hours, but what happens between day 5 and day 10 when that AUC may not still be within those errors?

DR. RELLER: Thank you very much, Dr. Leggett.

On the points that Dr. Leggett addressed his perspective others who wish to comment on any or all of those and how they influence your thinking on the vote that we will take?

Dr. Ebert?

DR. EBERT: Just one expansion. Dr. Leggett mentioned the issues about AUC and much of that information was developed in animals and that total daily dose whether it was given in single or divided doses showed equal efficacy and again, I share his concerns for two reasons. One is that that data was based on microbiologic response, not clinical response, in other words number of organisms eradicated in the animal models. I have not seen a similar corollary to that in a human infection model if you will and then secondly, again, the concerns about how far can one really extend the dosing interval and still see adequate bactericidal effect.

DR. RELLER: Dr. Chesney?

DR. CHESNEY: I, also, have a real concern about the vomiting in the first day because particularly for infants that comes at a time that they often have high fevers and are already vomiting and not taking anything orally and perhaps dehydrated, and to give them a very high dose of a drug that is conjugated in the liver and to add vomiting on top of that may necessitate hospitalization. So, that is another area that I have some anxiety about.

DR. RELLER: Dr. Wald?

DR. WALD: I think we have a tremendous dilemma here this afternoon because we heard some excellent presentations this morning about all of the parameters that influence outcome in acute otitis media and I think that they really highlight some substantial weaknesses in the studies that are presented today, especially the clinical only studies and especially because the age group that was focused on was older children rather than younger children, and I think that the microbiologic data are weak.

I will restate again a 50 percent retrieval on patients in whom one is very anxious to make a correct diagnosis is very low. Most tympanocentesis studies have recoveries of between 70 and 80 percent for positive microbiology.

So, if a positive microbiology is seen in 50

percent of those patients who I presume are highly selected because you want them to be positive, then I think we really have to worry that the number of children who actually had acute otitis media in the remaining clinical only studies was really substantially lower than 50 percent and so I think these are sort of the facts.

On the other hand these are not standards that we have held other products to, and so, I think that the real focus is do we have a new standard that we use this afternoon or do we create a new standard which I hope will be the subject of our discussions later this afternoon and what do we do with this product at this time? So, I think it is a tough dilemma.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: I have concerns, also about the analysis. I mean we didn't talk about the fact that what was called a modified intent to treat is not intent to treat by any definition I have ever seen before. The people who didn't show up for the day 28 or whatever the definitive test of cure whenever that was, the ones who didn't show up were simply left out. They were not involved in the analysis.

Now, that creates, missing data always creates a real problem. If they were, indeed, failures for whatever

reason, those success rates, those cure rates that we were seeing are even lower than the numbers that we were given.

In some of the studies those were very substantially missing including ones that were used for labeling; the studies for the 5 day that were used for labeling had very substantial missing data.

I am concerned that maybe what we know ain't so. This really is a worrisome thing. So, I think that the actual success rates are lower than we have been told in these presentations.

DR. RELER: Dr.Christie?

DR. CHRISTIE-SAMUELS: I have several concerns and some of them were already outlined. However, one includes the representational children are the age 2 years where there is a higher likelihood of failure and I am not so sure that the role of Hemophilus influenzae type B has been clearly outlined.

We heard some data from Costa Rica. I realize it is true that here in the United States the patients are likely to be immunized. We are actually using a very, very young age group and since they are using a drug where you may have resistance to HiB I am sort of worry about that. I am worried that the recovery rate for bacterial pathogens was less than 50 percent and I am worried, I am concerned

that the PKPD data was not available, especially for young children and the data that was presented I am not very clear on what was presented but the data that was presented for those who vomited as far as I can understand that data was for adults not necessarily children. So that to me has not been clarified.

The Pollyanna syndrome I wonder how much of that is being shown in the data that was presented here. One of our presenters showed us that efficacy needs to be more than 90 percent if we are going to say that it is significant, and I think the ethical dilemma for us on the Committee is I think the sponsor was given a guidance document which I think they followed, but based on the presentations, the three presentations that we heard from Dr. Marchant and the two public presenters the question in my mind is should we include, since we are now changing the standard should we, as a Committee look at the total picture based on what the guidance, what guidance they were given alone or should we, also, include what we heard today, and I think that needs to be clear to us because if indeed we are to include what the three speakers said, well, then I think I might, well, we will see how the afternoon passes.

DR. RELLER: Dr. Christie has pointed out some of

the dilemmas that the Committee faces. One thing I would like to clarify is that it seems to me important that we all understand that whatever vote the Committee takes is not an issue I don't believe of whether the sponsor followed the existing guidelines or not because we must assess the safety and efficacy based on the study requirements that the FDA heretofore has provided as guidance for industry.

At the same time following those guidelines the Committee is asked in their view based on the data presented from the sponsor and from the FDA whether the information available is sufficient to make them comfortable if you will about the safety and efficacy of either a product or an indication or a dosing regimen of an existing product and we will get there eventually.

Dr. Chesney?

DR. CHESNEY: Another issue for me and I would like to reiterate what Ellen and Celia and Dr. Reller have said in terms of how do we make this decision and I think Dr. Reller has clarified some of that, but one of the other concerns for me is that this is not clearly a better drug than what we have. It has a prolonged half life which means that the concentrations are going to decrease and decrease and decrease with time which we have heard over

and over again is the way that you develop drug resistance and we already have high levels of resistance to the macrolides and are we only going to be contributing to the problem by approving a drug which is not clearly better than what we already have out there with a number of unknowns of which I think I pointed out that the absence of pharmacokinetic data is another piece to the puzzle.

DR. RELLER: We have heard much discussion from the right side of the, my right side of the table and I am delighted that Dr. Patterson has her hand up from the left side, my left side.

DR. PATTERSON: Okay, I just wanted to make a comment regarding the resistance issue. Based on what we do know about the pharmacokinetics of azithromycin and granted we don't know about the single dose in children, but there is data to suggest that the efficacy would be based on the area under the curve over MIC ratio with this drug as compared to even the other macrolides and certainly the beta-lactam antibiotics, so that with a single dose you know it looked like certainly compliance was better but also it might have, you know, less effect on selection of antibiotic resistance, specifically macrolide resistance than the 5-day regimen if you were just giving it as a single dose, and I wanted to make a comment, too, about the

Pollyanna phenomenon which I think is a real one but I think that it is not unique to acute otitis media.

Having been involved in some of the vancomycin resistant enterococci studies when before we had options for therapy we found that all but the or many of the patients except those with very severe infections had some spontaneous resolution, so while I think it is a phenomenon I don't think it is unique to otitis media, and the other issue about the resistance is that I found it interesting that with the strains that have the efflux mechanism which is the most common type of resistance in the United States that six of eight of those patients responded anyway even though the MIC was eight.

DR. RELLER: Dr. O'Fallon and then Dr. Wald.

DR. O'FALLON: One of the things that is making it difficult for the Committee is the fact that we are back to the business of having point estimates. Six out of eight is 75 percent. The trouble is that the confidence interval, any confidence interval you want to choose is going to be so broad with only eight people that it is going to be consistent with response rates running from about 35 percent to practically 100 percent.

So, I worry. I am going to come back and say again, I think it is very important that we see confidence

intervals and I want to commend the company for presenting that nice thing that I asked about because I didn't understand it the first time I saw it, but that is the way I think that we should be seeing response rates for any of the ways you define response.

We should be seeing how they line up with everything else and it will give us a feeling for how big the study was and how big the population was.

The problem for me with this whole thing is I don't know how to put this politely; so it is just going to be bald. The guidance as written now rewards sloppy research. If you use a clinical end point without doing any kind of a tap that is the -- and then you throw away the people that just didn't show up at the 28 day you can really manipulate your success rates way up there, and then if you don't take into account the major prognostic factors of the subsets of people that have different responses innately in the disease, if you don't take into account those things, you can make your drug or your agent look good, and I am afraid right now I think the guidance is wearing a black hat in this whole issue today. It was before I came in here and I am even more convinced of it now.

DR. RELLER: Dr. Wald?

DR. WALD: I think that Dr. Patterson really raises another important generic issue for our consideration. In the year 2001, when we heard data that 25 to 35 to 40 percent of *S. pneumoniae* are resistant, shouldn't it be our expectation that that number of *S. pneumoniae* isolates in the clinical study will be resistant? Are NC microbiologic data addressing that particularly? I know we had a lengthy discussion about high-dose augmentin around the issue of resistance, but resistance is now an everyday phenomenon. It is not a special phenomenon. It is what we are treating when we treat acute otitis media so that we really have to have an adequate complement of those cases, I think in order to make a judgment, and I have to say that Joan has really highlighted the issue of toxicity and hepatic metabolism.

Why do all these studies start at 6 months? Surely the drug is going to be used in children under 6 months of age. Is that our requirement? Why do folks start at 6 months? Does anybody know?

DR. ALEXANDER: This is Dr. Alexander. I am actually doing a presentation a little later that sort of addresses that a little bit, and from what I was able to research in looking at our previous guidance and the points

to consider document and such, they were looking at children that were greater than 6 months of age because of concerns about actually being able to accurately diagnose for the purposes of clinical trials the acute otitis media in those children that were less than 6 months of age, that they had concerns due to, I think some related to the organisms that were identified from children that were less than 6 months of age and some actually related to the physical examination, being able to accurately diagnose infection in that population.

DR. WARD: Just the last issue that I would mention is the one about duration of therapy, and I think that there is a controversy about 5 days versus 10 days and again, do we have any -- and I think the data support the notion that short course therapy, 5-day therapy is disadvantageous in children under 2, and we would expect that because they are more difficult to treat. So, is there any reasonable expectation that the single dose of azithromycin will have a level beyond the fifth day of treatment? Is that known? If a 30-milligram-per-kilo dose is given on day 1 is there anything on day 6?

DR. RELLER: Dr. Gorman?

DR. GORMAN; I would like to echo Dr. Chesney's comments about toxicity. Known tentatively to be

intracellularly concentrated it presents some concerns about the young infant in terms of this dosing, and the resulting need for PK and PD data, also, in children less than 6 months or let me say over the entire range in which this will likely be used in the ambulatory setting which would be from birth to the end of the pediatric age range will be likely.

I look at the Pollyanna effect as the fact that you are using this chemical that you call an antibiotic inside a host that has a huge number of other resources that it brings to bear or gets in the way of taking care of this infection, and one of the things that was not clear to me when I read the article, while the Pollyanna effect will make a bad drug look fairly good, it, also, prevents a good drug that is not being used from looking bad.

So, if you take the best known drug, and I will use an old example of an oral antibiotic that was unpalatable that people would take and then throw up and then the patients would not take it again, you would still get the same results.

Things would look good on this data presentation because of the Pollyanna effect which would not even let the best drug when not used effectively, when not used compliantly still look pretty darn good.

I cannot underestimate for my parents, however, how important compliance and tolerability are in the dosing of these agents, and the concept of trucking around from work to day care to home different antibiotic agents becomes an incredible financial burden for these people, and if there was any data that just got them back into day care faster it would be a huge clamor for this medicine much like there is for the injectable medicine in our community, injectable alternative.

Host factors you cannot control for but in any new guidance might be considered might make the studies impossible to do, but you need to start looking at those things as either subclasses statistically as you do your analysis or excluding them from the enrolles so you know who is in the population.

Since these are short studies in terms of each individual's participation you should be able to figure out who is in day care and who is not, who had siblings and who did not.

Lastly on the guidance I wear another hat. I sit as an IRB member on two different IRBs and we would not approve the tympanocentesis study for otitis media under any circumstances. We feel it is not the standard of care. We feel it puts children at risk for a disease which has in

2001 basically no sequelae.

DR. RELLER: This is a great opportunity to hear comments from the Committee after we hear from Drs. Alexander and Soreth about the importance of the single tap studies as regards the data presented in evaluation of the product on the table.

Dr. Alexander?

DR. ALEXANDER: This was actually just a question as a point of clarification for Dr. Gorman's statement. Were you saying that any study with tympanocentesis would not be approved or were you referring specifically to the double-tap studies?

DR. GORMAN: It would be very difficult in the university or community IRB that I sit on to have a, in fact, we have turned down single-tap studies because they appear to offer no scientific benefit to that child, and they pose a risk. So, it adds risk with no benefit, and I have had the opportunity to talk to the chair of an IRB in another large institution who, also, claims that he routinely rejects all tympanocentesis studies.

Now, clearly some IRBs are accepting them because they are still being done.

DR. RELLER: Dr. Chesney, and then we will come to Dr. Maxwell.

DR. CHESNEY: I just wanted to comment on your comments. I could argue very strongly that a tympanocentesis study offered distinct advantages to the child because you know what the organism is. You know what the susceptibilities are and you can narrow your spectrum based on that.

So, just a comment, not immediately relative to the issues at hand.

DR. GORMAN; Our IRB would disagree. It offers advantages to science. It offers not advantage to that child because you are not going to change the drug inside a clinical trial unless you then set up the trial to do that which we have not seen yet.

DR. RELLER: Dr. Maxwell and Dr. Wald.

DR. MAXWELL: I just had an additional question. To my question as to how many children were redosed who vomited in the first half hour the number was eight, but I really wonder how many children vomited 1 hour, 1 hour and 1/2 and 2 hours after and then were redosed, and I don't know if anyone here has that answer.

DR. RELLER: Dr. Dunne may have or will have, and we will come back to him when I see a hand.

Dr. Wald?

DR. WALD: Maybe not to belabor the

tympanocentesis discussion, I think there can definitely be benefits to the patient. There is immediate pain relief even though there is some experience of pain at the time of the procedure. I watched one just yesterday afternoon, and then we did have a sample, and we could if we need to make a precise judgment about non-response to that therapy we will have information in our hands which will be invaluable.

So, I think that one can justify it in those terms and some children are, of course, experiencing quite a lot of pain and for those children it probably is a bigger benefit.

DR. RELLER: Dr. Marchant?

DR. MARCHANT: To make a comment in response to Dr. Gorman that adds on top of what Dr. Wald just said about tympanocentesis, the problem is if we don't do tympanocentesis we won't know what is going on at all in drug approval and that means that it will sort of bring to life the Pollyanna phenomenon that poor drugs with poor efficacy get licensed and we don't know that they don't work. We don't figure out that they don't work and out there in clinical practice there are going to be patients that remain symptomatic because we have approved and then as practitioners prescribed drugs that are less efficacious

and so to abandon tympanocentesis is to basically put ourselves in the dark in terms of the performance of antimicrobial agents for this disease.

DR. RELLER: Dr. Gorman?

DR. GORMAN: I am sorry I brought my IRB into this. First of all, I don't own this IRB. I just sit on it, and while I don't disagree with the scientific arguments here, you are now in the position of having your own data used against you that has been developed by typanocentesis.

Your predictive value when there is bacteriological cure is excellent in terms of clinical cure. Your predictive value when there is not bacteriological cure is a coin flip or perhaps a little bit better than a coin flip.

So, one would have to argue at least in the data presented in one of the articles that if you didn't have a bacterial cure, a clinical cure was still a 50/50 outcome or roughly a 50/50 outcome, and I understand the other clinical parameters that come in here.

The second thing that your tympanocentesis has shown me to sort of mute what Dr. Wald and you have just said is that often when you retap these people they have different organisms. So, how exactly are you going to then claim you need to retap them each time they have a

reoccurrence because I am going to then be in the position I have data that shows me from previous taps that clinical failure doesn't necessarily mean the same organism is present.

DR. MARCHANT: Clinical failure is during therapy when you switch from one organism to the other. Yes, they do occur, but they are way the minority of failures. It is a very small number you are talking about.

DR. RELLER: Thank you, Dr. Marchant.

Dr. Glode?

DR. GLODE: I have really two separate issues to mention. One would be that abstract I gave you. Would this be an appropriate time about unanticipated adverse effects or not?

DR. RELLER: Sure. We want to get all of the discussion out on the table before the vote. Please?

DR. GLODE: Okay. I just wanted to mention this briefly because I don't think it is relevant to the vote today, but it is relevant to the issue of large studies and large study subjects and perhaps unanticipated adverse events, and that is that this abstract that was published in the Infectious Disease Society of America, and I just happened to be at the poster because I happened to be at the meeting whenever that was a week ago, and I happened to

know I was coming to this meeting, and it was about azithromycin. So, I was paying more attention than I might otherwise, but it is really interesting for both, I think the FDA Advisory Committee, the FDA and the sponsors, and it is just an article looking at azithro or an abstract exploring in an animal model azithromycin as an immune modulator and in the animal model when you give azithromycin and you follow with a conjugated pneumococcal vaccine you have a very statistically significant effect on the immune response to that vaccine.

That, of course, is very important to me if it had any application to human beings, and we don't know that it does, but someone should look at that and make sure that there is not an immunomodulatory effect in children because I actually personally am more interested in preventive invasive pneumococcal disease than anything else to do with otitis media.

So, I really, you know, would just want that to be explored and obviously this is only in an animal model. So, it may not have any relevance to humans, but is nonetheless interesting scientifically, and so, I just wanted to bring that to people's attention so that it is something people look at perhaps in the future studies.

Then my comment about the information that we

were presented with is I keep sort of focusing on the less than 2 year old even though that was not the majority of patients enrolled in these studies but may be the majority of patients with otitis from what we have heard about, and if I look now at day 28 failures with single-dose azithromycin it looks like it is in the range of 24 percent, with 3-day 33 percent, with ceftriaxone 30 percent, with augmentin 49 percent. So, again, I mean I really don't like any of those clinical failure rates in the less than 2 year olds. That is sort of with all comers, and then if you look then specifically for *Hemophilus influenzae* in the less than 2 year old where it was in the sponsor's study, a 47 percent clinical failure rate at day 28, and I was trying to put that together with the Dagan published study where they concluded that azithromycin was inferior, but in fact they are very similar because that is 42 percent for *Hemophilus influenzae* clinical failure rate in their study which had a mean age of 16 months. So, it probably fits. I mean probably the data is in fact not discrepant; it is similar. They just reached slightly different conclusions, but it helps me that the data is, in fact, sort of concordant.

So, I have to say that compared to ceftriaxone or augmentin it looks like it is in the same ballpark even

though it is a high, if you will clinical failure rate overall, but I guess that is just what we have in less than 2 year olds with otitis media.

DR. RELLER: Dr. Dunne, do you have some additional information for our consideration?

DR. DUNNE: Yes, I wanted to come back up and tell you about the children who vomited within the first 2 hours and how they did with redose.

May I have the first slide?

So, these are patients who received a single dose of azithromycin who vomited on day 1 after this first dose. This population is all the patients that received that dose, 487 children and those who vomited are listed here in yellow. We broke it down by the study from which those children came.

You can see with 30 minutes there were eight. They all occurred on study 1015 and all eight of those were redosed. There were 4 and 10 children four below the age of 2 and 10 above the age of 2 who vomited within 2 hours.

This includes this group, of course. That is why the fours match up here. So, six additional children over the age of 2 who vomited in that 30-to-120-minute interval.

We do have children who vomited, and we don't have the exact time of that vomiting. We know that they

were not redosed except for this one child.

Next slide?

Now, how did they do? Okay, we said that there were eight children who vomited within the first 30 minutes. We had outcome data on seven of those eight children under the age of 2. All three of those children were clinically cured at end of therapy and again at the test of cure visit. Of those greater than 2, three out of four were cured. At test of cure one out of four were cured.

The next slide is what happened between 30 minutes and 2 hours. This would have been children that vomited in that interval but did not get redosed. There were no children less than 2 in that category, four out of six both at end of therapy and test of cure were cured.

There was one other point that was made about the what do we do with the missings, and typically you might, well, one way you might handle the missings is by calling all of them failures and seeing what happened to your comparison.

If you could put up that slide, please?

This is the only study that had a significant number of missing and by significant it is in 8 to 10 percent something range. It was R-0581. The other ones had

two or three people missing. So, it doesn't really impact much, and this would be an analysis where we set all the missings to failure on each arm, and you see the success rate at day 14 is 80 percent and 82 percent on azithromycin and amox/clav. The lower limit of the confidence bound is minus 11.

At day 28 success rates are 66 and 67. Lower limit is minus 12 on the difference, similar rates for cure. Lower limit is minus 8. These are within a point of the lower limit from what we saw before when we had just excluded the missing. So, we didn't see anything really different. We did sensitivity analysis by setting the missings to failure in all the studies, but as you can imagine it doesn't really change anything very much.

DR. O'FALLON: But what bothered me when I was reading this and doing this was the fact that the Pollyanna effect under those circumstances, you know, for the mix, particular mix of patients, tap water produced 71 percent at test of cure.

So, here we have numbers that are well, I mean percentages that are well under 71 percent.

DR. DUNNE: Yes, I mean I think we don't as you could imagine, the studies that we do are comparative studies to approved agents. So, the issue about comparisons

to placebo, that would be a different kind of forum where that would be probably addressed. I think the best that we can do to help people get comfortable that at least azithromycin is as effective as amoxicillin/clavulanate when you start to get the numbers up was on that kind of meta analysis thing.

If we can just show the slide, pick either one, the day 14 main presentation tornado chart there? I will just come back to that here.

That would be Slide 115 in the main presentation. Again, we won't be making comparisons to placebo. We would make comparisons to what we think is an active drug which would be at least amoxicillin plus a beta-lactamase inhibitor and over the course of looking at 4000 patients we see point estimates of difference that are in the range of 1 percent.

So, if people are comfortable that at least amoxicillin is something better than placebo after looking at 4000 patients with these clinical end points; these are clinical end points; this is not the bacteriologic end point, it is at an earlier time point. Once you start adding up all the patients and all the trials which I would say that you probably don't get a chance to see this data very often because it is not often that you see a drug

coming here that has already been out on the market for 5 or 6 years and has a lot of experience; so, this is an opportunity to see a lot of patients in a comparison like this and it looks to us like the azithromycin children did as well as the amoxicillin/clavulanate within very narrow confidence bounds.

DR. O'FALLON: When you showed that this morning I looked at it and I saw the azithromycin versus amox/clav as being almost significantly in favor of the comparator. That second one up from the bottom, it almost excludes, yes, the confidence interval almost excludes zero. So, it looks to me like that is even saying that it is worse.

DR. DUNNE: The confidence interval would say that it is within the bounds. So, it is hard to say that it is worse, but if it is different it is less than 1/2 percent.

DR. RELLER: Dr. Cross?

DR. CROSS; Dr. Chesney brought up the issue of giving a single large dose which is accumulated or conjugated in liver. Do you have any data on liver function in the single high dose?

DR. DUNNE: Yes, in study 95-001 where we looked at a single dose of azithromycin, the 3-day dose and ceftriaxone we did collect laboratory exams during that

study.

Let me see if I can pull that slide up?

Slide S21, please?

Again, there were 66 children in this study at baseline. We have laboratory exams on most of those children, most but a few. Looking at neutrophil counts ANCs less than 1000 there didn't seem to be any difference between any of these regimens. Total bilirubin, the same pretty much across all. AST and creatinines again, no abnormalities seen in that particular group, and this would be consistent with the sum of experience we have had now with all the patients that have been treated with a 5-day dose.

The regimen 1, 3 or 5 will accumulate to the same degree. The AUCs are very similar in each of those regimens. So, the same total amount of drug will pass through the liver and as people are probably aware a small amount of azithro is metabolized in the liver. It is not a drug that is really active to the P450 system. So, in fact, it doesn't really get metabolized much there.

The experience with 5 day, looking at total dose should be similar to the single dose, and we do have a small patient population here to give you a sense of labs.

DR. CROSS: This is entry or --

DR. DUNNE: This would have been at the day 7 to 8 visit. If anyone had an abnormality later though; they came back with another problem, that would have been picked up, but this would be in the earlier, yes, that is my understanding.

DR. RELLER: Dr. Chesney?

DR. CHESNEY: How old are the children from whom you got that data?

DR. DUNNE: The mean age of the children in that study was about 2-1/2 years with a range from 1 to about 4.

DR. RELLER: Dr. Ebert?

DR. EBERT: My question is again directed towards the vomiting that occurred in some of these children who received a large single dose. Certainly in adults who are given excessive doses of macrolides one has the potential for at least a reversible degree of ototoxicity that can occur and I am wondering you look at all in any of these children at any impact of the drug on vestibular function or hearing? Could that have contributed to the vomiting or was it thought to be a gastrointestinal phenomenon?

DR. DUNNE: Okay, so the question speaks to the association of macrolides and ototoxicity, and are we in that range, for example, in these kind of RTI doses.

About 3 to 4 percent of adults that receive doses

in the AIDS program; so, this was much higher doses, for example, 600 milligrams a day for life essentially, about 4 or 5 percent of those people would develop some kind of a reversible hearing impairment, but the earliest that we really saw any kind of hearing impairment occur in that population, the earliest of that 5 percent was about 10 grams and the median amount was about 40 grams. So, it is well beyond what we see here, and that is consistent with what we know from the 5-day program where we really haven't seen any ototoxicity occur.

We didn't do hearing tests during this program. That is an interesting thing maybe for efficacy end points, actually in otitis media studies, but we didn't do that in any of these programs here.

DR. RELLER: Dr. Patterson?

DR. PATTERSON: I was going to ask you about the vomiting. Was that just a single episode? Were there any instances of persistent vomiting and, also, the patients who were redosed, did they vomit?

DR. DUNNE: The way we collect the side effect data is by dates. So, if you have an episode of any adverse event we just list the date down there, but on questioning to the coordinators this is generally something that happens one time. There was, and I should, also say that

when we look at the mild, moderate, severe assessment of all these side effects 80 percent of the vomiting was mild. There was 20 percent moderate. There were no severe vomitings which we interpret as being persistent and recurring although the investigator is able to assess that for himself, and the other question was did they revomit after redose?

DR. PATTERSON: The patients who were redosed.

DR. DUNNE: Yes, there was one of those eight children who did actually vomit again on the redosing, and then they got amoxicillin, I think after that..

DR. RELLER: Thank you, Dr. Dunne.

DR. ALEXANDER: Related to the vomiting, sorry, Dr. Alexander. Related to the vomiting I actually think that there were two patients that were within the non-comparative study who vomited who were redosed and then one of them, both of them vomited again and one of them or both of them received amoxicillin, I believe. One of them was excluded from the MITT analysis as being considered to have vomited all the medicine that she received, so was treated as though she never received any medication within the efficacy analysis of the study.

The other one, I believe, was included as a failure because of receiving amoxicillin instead.

DR. RELER: Dr. O'Fallon, you had a comment?

DR. O'FALLON: You see that is the problem with leaving people out. That child, yes, didn't get treated, but couldn't get treated and therefore should be considered a failure instead of left out of the MITT analysis, the one that was left out.

DR. DUNNE: I would have to go back and check on that other patient. I cannot really comment on that right here.

DR. RELER: Dr. Goldberger?

DR. GOLDBERGER: I thought perhaps before the vote actually occurs it might be useful to make a few comments about this issue that came up about what guidance ought to be utilized in terms of thinking about the voting.

You know, I think obviously as a starting point the first thing to do is to make a determination in terms of the recommendation you are going to provide, is this product safe and effective based upon the current guidance that exists. Concerns have been raised about the amount of pharmacokinetic data and other issues, and clearly the expectation is you will take these matters into account in making your vote.

Then the issue has come up as well about the fact that it would appear as though the current approach to

development of products in this area may have certain limitations, and I think it should be obvious to everyone, you know, that we certainly recognize this as well, both in terms of our asking you to comment on some of the things that were important to you as part of question 1 as well as in the fact that there will be some specific discussion about this later in the afternoon.

On the other hand there has been some discussion in the last few minutes about what studies can and cannot reasonably be performed, and I think that one needs to take into account that if one takes a new standard as the de facto standard involving studies in which there is legitimate disagreement as to whether they can be performed that obviously poses certain problems.

In addition, there has been some important PKPD data presented here today that may well be very influential in subsequent guidances, but may require some additional review before one can reasonably conclude that it should become the standard.

So, I think that you are free in the end, obviously to make the recommendation as you see fit. We do, you know, like to understand your thinking, and you should be aware there can be a situation in which our regulatory requirements may require us to think a little more in terms

of exactly how to utilize your recommendations given that there may be some difference between what we would like to be able to do in terms of developing drugs and what the current standards are today.

I hope that helps you a little bit in thinking in terms of the voting.

DR. RELLER: Thank you, Dr. Goldberger.

I propose the following. We will go starting at my right with Dr. Wald and ask for since some of the part 2 and the subsets of the questions require this delineation for Committee's advice to agency that we simplify it to single dose 3 day and give us a yes or a no for each and if it is yes for a single day, if you want to add any caveats as Part A delineate please say so, and if the answer is no, any additional studies for single day and then go to 3 day with the same comments and then we will take question No. 2 depending on what the majority view is from the initial vote.

Two yeses or no's and plus or minus comments related thereto.

Dr. Wald?

DR. WALD: I guess what I would conclude is that both the single day and the 3-day regimen compared favorably to the comparator drugs in a study design which

would not allow us to easily distinguish a better from a worse drug but that this has, in fact been the standard by which we have judged drugs, and so in that context I would say that the data support the safety and efficacy as we have until now interpreted it, and so that would be a yes, yes, without caveats.

DR. RELLER: Thank you.

Dr. Leggett?

DR. LEGGETT: Yes, for single, yes, for 3 day, no caveats.

DR. O'FALLON: No, for both. I don't think that the evidence we see has established the effectiveness or safety actually of either.

DR. RELLER: Dr. Christie?

DR. CHRISTIE-SAMUELS: I have to say a no for both.

DR. RELLER: Any additional studies, Dr. O'Fallon or Dr. Christie with your no votes?

DR. O'FALLON: Yes, I think that the bacterial studies although the two in the literature are some start, but I think there should be those and then for definitely sure the PK studies in the younger children, maybe even PD but certainly PK in the younger children before we can approve it, because that is apparently the majority of

these patients. I think we should see evidence in those patients.

DR. RELLER: Dr. Christie, a part B comment for either or both 1-and-3-day regimens?

DR. CHRISTIE-SAMUELS: PKPD data, larger Ns looking at ototoxicity and hepatotoxicity, children younger than 2 years of age, studies in day care centers and Dr. Dagan's comments, the second to last slide for hand-tailored AOM drug studies. I think he summarized it pretty well.

DR. RELLER: Dr. Chesney?

DR. CHESNEY: I would say no for the single dose because we have no pharmacokinetic data and this is such an appealing dose form. It is 100 percent compliance in the office. It will be used instantly for all ages, and I have problems with that.

I would say yes to the 3 day regimen because it is already being used 5 days, and I don't think 3 days is that much different but only for children over 2 years, again, with absent kinetic data.

DR. RELLER: Dr. Ebert?

DR. EBERT: Yes, for single dose, yes for 3 day regimen. I do believe we need to do a better job of measuring or comparing response in agents earlier in the

trial period and not waiting for 28 days to assess outcome.

DR.CROSS: While the data are not optimal I think it would be helpful as has been brought out by other Committee members to have some better data on children less than 2 years and have better PKPD data, I think within the context of the guidelines and its equivalence or at least no difference with comparators I would vote yes for the 1 day and yes on the 3-day regimens and no caveats.

DR. RELLER: Thank you.

Dr.Gorman?

DR. GORMAN; I would vote yes n the 1 day and yes on the 3-day dosage of this form. Caveats is such a broad terminology. What caveats are we allowed to put on the label in terms of the question of tympanocentesis? I am looking for guidance on the caveats that are allowed under your regulatory statute.

DR. SORETH: I think that what you can take into account are issues of age, if you feel that there are data to speak to differences above and below the age of 2. Caveats have at times been put into labels not only for otitis but for other infections as well that some organisms, patients with some organisms recover better or have different rates of success than others.

DR. GORMAN: I would then put in a caveat that

this drug not be approved in children under 6 months of age until the sponsor company can provide PKPD and toxicity data in that group.

DR. RELLER: Dr. Glode?

DR. GLODE: I would think that the data do support. I am going to divide up safety and efficacy for just a moment. They do support efficacy of the single dose and of the 3-day regimen compared to the licensed products.

I will, also, support it with regard to safety mainly on the issue of 40 million doses distributed to people of different ages and presumably having been used safely, but I am disappointed that there were not actually more laboratory values for us to look at with regard to safety issues and certainly the absence of PK data was, also, concerning.

DR. RELLER: I would vote no to both 1 day and 3 day based on the paucity of pharmacodynamic data on the 1-day dose and with the 1 day and 3 day where the bacteriologic confirmation is available with one of the studies and the other it is the pharmacodynamic, and I think that the total database though the efficacy by the past criteria is comparable I think the database could be more solid when we go to these new dosage regimens, and it is just not all fitting together for me for either the 1

day or the 3 days. So, my vote is no for each now. I think additional studies are needed before approval of those regimens.

So, what we come out with is six to four for single-day therapy and seven to three for 3-day therapy which enables us to go to question 2 for the single dose regimen. We will come around the table in reverse order, starting with Dr. Glode. What advice on it if any should be given regarding the issue of vomiting associated with the 1-day regimen? This is information for prescribers and patients that presumably would move its way into a package insert, advice for the agency to consider in their final decisions on the issues at hand.

DR. GLODE: Okay, advice for the agency to consider, perhaps a statement that says that with the single dose of azithromycin an increased rate of vomiting has been observed and then I suppose some comment should be made to prescribers about under what conditions and how many times the drug should be recommended to be redosed, and I really with N equals 8, I don't know that I could come up with that. I could make up something. If the patient vomits within 1 hour you may redose times one, but that is as far as I can go.

DR. RELLER: Thank you.

Dr. Gorman?

DR. GORMAN: My recommendation would be more in terms of packaging, much like syrup of ipecac in the past. I would make sure there were two effective doses for the largest child that you would expect to require liquid. So, in ipecac if the first dose was not successful you administer a second dose. In this case it would be exactly the opposite. If you vomited the first dose I would like the packaging dispensed by either the pharmacist or the physician to have enough for the second dose available so that the rescue dose would be available to the parent without another trip to the pharmacy at no added expense.

DR. RELER: Dr. Cross?

DR. CROSS: I think, also, that there ought to be some comment about the need for redosing if there is vomiting within a specified period of time and on the other hand we don't have enough data on that to actually make that recommendation. So, I think we have to urge the sponsor to acquire that so it is included on the labeling.

DR. RELER: Dr. Ebert?

DR. EBERT: I agree that there should be some window at which vomiting before that time would require redosing and vomiting after that time may not require redosing. As the previous panelists noted I am not sure

that we know the exact time frame for that window, and I concur that if at all possible at no increased cost if we were able to give an extra dose that would certainly save from a consumer standpoint an additional trip.

DR. RELLER: Dr. Chesney?

DR. CHESNEY: I don't think we can make any recommendations. If this is absorbed well in the first 20 minutes and then the child vomits and we give another dose now we are talking about 60 milligrams per kilo as a single dose, and if I was nervous about 30, I am really nervous about 60. So, I don't think we can make any recommendations.

DR. CHRISTIE-SAMUELS: May I seek some clarification please? I have a question. The recommendation is from the Committee, if the Committee recommends that it be approved or is it --

DR. RELLER: I will give you some help, Dr. Christie. I voted no, and consequently I have no additional advice because Dr. Chesney summarized and that was one of the considerations in voting no because I simply didn't know enough about what to do in the 10 percent who vomited, and I think there are sufficient issues regarding safety that without the pharmacodynamic data and the group in greatest need if bacteria would be demonstrated on a tap,

and it is not there for me, and it is one of the considerations.

Now, you can comment or not comment.

DR. CHRISTIE-SAMUELS: Thanks for the clarification. I guess I have to abstain since I didn't make the recommendation in the first place.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: I, also, did not make the recommendation, but I would like to point out that I don't think there is any evidence or at least certainly not adequate evidence to try to make a decision on this. There is not enough here to make a decision, at least from my perspective.

DR. LEGGETT: I would like to point out the fact that many parts of the world don't even use antibiotics for acute otitis media much in the same age group as these folks. So, the only thing I would say is just note that increased vomiting is seen with the one dose and not say anything about redosing.

DR. RELLER: Dr. Wald?

DR. WALD: I think that we have to let common sense guide us here and that we would certainly give advice or we would let people know that increased vomiting is observed and I would say that it is reasonable that if the

child vomits in the first 30 to 60 minutes to repeat the dose.

DR. RELLER: Dr. Soreth, can we provide any additional information to clarify what we want to convey with questions 1 and 2?

DR. SORETH: Yes, Dr. Reller. There were several comments from Committee members and guests with regard to additional studies for PK and PD. Could I just get a little clarification about what those would entail?

DR. RELLER: Dr. Chesney?

DR. CHESNEY: I feel that we need more information at least in the child under 1. I am just pulling that randomly, but I think as I mentioned before this is such an appealing dose formulation that it will be used in 1-month-old infants, and it may be used in 2-week-old infants, and we know that their excretion mechanisms both liver and kidney are not fully mature yet. So, I would guess if one had to limit the age groups for me it would be the lower age group that I would most like to see pharmacokinetic data on.

DR. RELLER: Dr. Burns?

DR. BURNS: I would say, too, that if you are going to put in a caveat about redosing after vomiting that you would have to do PK in patients who had been redosed so

you knew whether or not you were getting into a potentially toxic situation.

DR. RELLER: Dr. Chesney?

DR. CHESNEY: I don't know the circumstances under which kinetic data can always be collected, but if it could be done in febrile infants who are being treated who may have viral syndrome where the kinetics might be different than in a perfectly well child who might not be stressed, I think that would be very helpful.

DR. RELLER: Dr. Soreth?

DR. SORETH: Dr. Reller, you, also, made a comment after talking about the pharmacokinetics that you thought additional studies were needed. Did you mean outside the realm of PKPD or what were your thoughts?

DR. RELLER: We have bracketed one single dose and 5-day regimen and there are some extrapolations to the 3 day based on if the 1 day has the studies that involved bacteriologic outcome and then we have the data from the efficacy in use with the 5 days. I don't see the studies being done on each of the regimens is what I am trying to get at, so that the full database for each of the regimens is not the same magnitude number of patients, etc.

The studies are different with the different dosing regimens, the content of the studies available for

assessment, the design of the studies.

Dr. Ebert?

DR. EBERT: This will probably be an incomplete answer, but I noticed some comments about PK but not a lot on the PD side of things. I think ideally from a dynamics standpoint we would be talking about bacteriologic eradication as an end point which we really have not seen to date with this regimen to compare single dose and multi-dose regimens with regard to their bacteriologic efficacy.

The secondary issues, of course, would be those of toxicity, whether there may be an association between serum concentrations and adverse effects.

DR. RELER: That concludes Phase I of the meeting. We will take a 5-to-10-minute break very briefly for a stretch. So, those who are not staying for part 2 can exit and we will launch at 10 minutes of 3 into the discussion of the guidance document.

(Brief recess.)

DR. RELER: We will start this afternoon's part 2 session with the presentation by Dr. John Alexander and then we will address the question.

DR. ALEXANDER: Hello, my name is John Alexander, and now that we have finished the questions specific to azithromycin we would like to have sort of a continuation

of the discussion that we have had already today regarding the clinical trials of acute otitis media, and what I am going to try to present is a little bit of information about our guidance document.

I will start off with a little bit of history and I promise not to go all the way back to 1962 and detail everything in painful detail since then, but just to start out, the Kefauver-Harris Amendments to the Food, Drug and Cosmetics Act were just significant in that after 1962 was really when drug companies were expected to show evidence of efficacy as well as what they had been previously doing which was the safety of drugs, so that it is really in the sixties and seventies where we began to consider, well, how do we show what drugs are effective and actually most of the sixties and seventies were spent addressing what were called DESI reviews looking at already approved drugs and their efficacy.

So, it wasn't until 1977 that we had our first guidance document on the clinical evaluation of anti-infective drugs, and I wanted to pull out these two particular quotes from that.

Within that document there was only about half of a page that dealt with the question of acute otitis media and I thought these two quotes were reflective of the

overall tenor of that particular document, one saying that it is necessary to confirm the presence of exudate in the middle ear by pneumotoscopy(?) and needle aspiration to obtain fluid for culture, meaning that patients, they were looking at pneumotoscopy as a method for particularly accurate diagnosis of patients with acute otitis media and the needle aspirate in order to identify those patients who actually had bacteria on culture, and the other quote, in the absence of culture of middle ear fluid no specific claim can be made regarding the effectiveness of any anti-infective drug, and so what we saw after this guidance document in the seventies and most of the eighties for anti-infective drugs that were looking for a claim in acute otitis media was that we had certainly a smaller number of patients that were studied but in those patients that were identified in those trials, they had bacteriologic information on all those patients at baseline.

So, we move forward in time to 1992, and the points to consider document, and this quote should look familiar from the sponsor's presentation this morning that two studies were identified in the points to consider document, one a statistically adequate and well-controlled multicenter trial that establishes equivalence of superiority to an approved drug and a second open study